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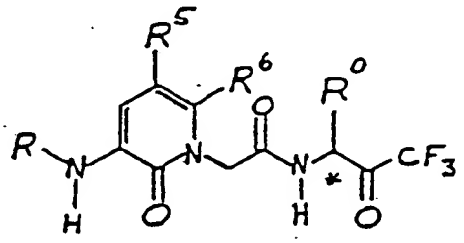

(I)

(57) Abstract

The present invention relates to certain novel heterocyclic compounds which are 1-pyridylacetamide compounds of formula (I), set out herein, which are inhibitors of human leukocyte elastase (HLE), also known as human neutrophil elastase (HNE), making them useful whenever such inhibition is desired, such as for research tools in pharmacological, diagnostic and related studies and in the treatment of diseases in mammals in which HLE is implicated. The invention also includes intermediates useful in the synthesis of these heterocyclic compounds, processes for preparing the heterocyclic compounds, pharmaceutical compositions containing such heterocyclic compounds and methods for their use.

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LACTAM DIPEPTIDES HAVING HLE INHIBITING ACTIVITY

The present invention relates to certain heterocyclic compounds, in particular, certain 1-pyridylacetamide compounds, which are inhibitors of human leukocyte elastase (HLE), also known as human neutrophil elastase (HNE), making them useful whenever such inhibition is desired, such as for research tools in pharmacological, diagnostic and related studies and in the treatment of diseases in mammals in which HLE is implicated. For example, HLE has been implicated in the pathogenesis of acute respiratory distress syndrome (ARDS), rheumatoid arthritis, atherosclerosis, pulmonary emphysema, and other inflammatory disorders, including airway inflammatory diseases characterized by increased and abnormal airway secretion such as chronic bronchitis and cystic fibrosis. Also, HLE has been implicated in certain vascular diseases and related conditions (and their therapy) in which neutrophil participation is involved or implicated, for example, in hemorrhage associated with acute non-lymphocytic leukemia, as well as in reperfusion injury associated with, for example, myocardial ischaemia and related conditions associated with coronary artery disease such as angina and infarction, cerebrovascular ischaemia such as transient ischaemic attack and stroke, peripheral occlusive vascular disease such as intermittent claudication and critical limb ischaemia, venous insufficiency such as venous hypertension, varicose veins and venous ulceration, as well as impaired reperfusion states such as those associated with reconstructive vascular surgery, thrombolysis and angioplasty. The invention also includes intermediates useful in the synthesis of these heterocyclic compounds, processes for preparing the heterocyclic compounds, pharmaceutical compositions containing such heterocyclic compounds and methods for their use.

In U.S. Patent 4,910,190, of 20 March 1990, assigned to ICI Americas Inc. (now Zeneca Inc.), there is disclosed a series of peptidoyl trifluoromethane derivatives which are HLE inhibitors. Disclosed herein is a series of substituted 2-(2-oxo-1,2-dihydro-1-pyridyl)-N-[3,3,3-trifluoro-1-(lower alkyl)-2-oxopropyl]acetamide derivatives, which unexpectedly possess inhibitory properties against

HLE, which provides the basis for the present invention.

According to the invention there is provided a Compound of the invention which is a compound of formula I (formula set out, together with other formulae referred to by Roman numerals, following the Examples) wherein:

R^0 is (1-5C)alkyl;

R is 2,2,2-trifluoroethoxycarbonyl or 2,2,2-trifluoroethylaminocarbonyl; or

R is a sulfonyl group of formula D.W.SO_2- in which D.W-, taken together, is hydroxy, amino, di(lower alkyl)amino, 2,2,2-trifluoroethylamino, 3,3,3-trifluoropropyl, 2,2,2-trifluoroethyl or trifluoromethyl; or

W is a direct bond, imino, carbonylimino, oxycarbonylimino or iminocarbonylimino; and

D is as defined below; or

R is a group G as defined below;

The group D or G is (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-3C)alkyl, aryl, aryl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)-alkyl wherein an alkyl carbon of G not bonded to the pyridone 3-amino nitrogen may bear an oxo group and wherein an aryl or heteroaryl moiety may bear one or more halogeno, nitro, methyl or trifluoromethyl groups and further wherein the group D or G may bear one or more substituents selected from a group consisting of hydroxy, lower alkoxy, lower acyloxy, COORa, CH_2COORa, CONRbRc, CH_2CONRbRc, $COO(CH_2)_2NReRf$, cyano, SO_2R^1, $CONRdSO_2R^1$, NReRf, NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCONRiRj, $NRkSO_2R^3$, SO_2NRlRm, $SO_2NRnCOR^4$ and $P(O)(ORa)_2$ in which

Q is oxygen or sulfur;

Ra-Rn are independently hydrogen, benzyl or lower alkyl; or, independently, a group NRbRc, NReRf, NRiRj or NRlRm is a cyclic radical selected from a group consisting of 1-pyrrolidinyl, piperidino, morpholino or 1-piperazinyl which may bear a lower alkyl substituent at the 4-position; r, independently, a group NReRf is a cyclic radical selected from a group consisting f 2-pyrrolidinon-1-yl, succinimido, xazolidin-2-on-3-yl, 2-benz xazolinon-3-yl, phthalimido and cis-hexahydr phthalimido; and

R^1-R^4 are independently trifluoromethyl, (1-6C)alkyl, (3-6C)cycloalkyl, aryl or heteroaryl in which the aryl or heteroaryl may bear one or more substituents selected from a group consisting of lower alkyl, hydroxy, lower alkoxy, halogeno or trifluoromethyl;

Each of R^5 and R^6 is, independently, hydrogen or lower alkyl; or

One of R^5 and R^6 is hydrogen or methyl and the other of R^5 and R^6 is a radical of formula B.Y- in which

B is aryl or heteroaryl, which aryl or heteroaryl independently may bear one or more of the substituents defined for D or G or an aryl or heteroaryl moiety thereof;

Y is a direct bond, methylene, ethylene or trans-vinylene; and

provided that no aliphatic carbon is bonded to more than one nitrogen or oxygen, except as part of a cyclic ketal or where the nitrogen bears a carbonyl group; or,

for a compound of formula I which is acidic or basic, a pharmaceutically acceptable salt thereof.

In this specification, the following definitions are used, unless otherwise described: Halogeno is fluoro, chloro, bromo or iodo. Alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such "propyl" embraces only the straight chain ("normal") radical, a branched chain isomer such as "isopropyl" being specifically referred to. Lower alkyl and lower alkoxy refer to radicals containing one to about four carbon atoms. Lower acyloxy refers to a radical containing one to about five carbon atoms. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative r ne derived by fusing a propenylene, trimethylene or tetramethylene diradical thereto, as well as a stable N-oxide thereof.

It will be appreciated that, owing to the asymmetrically substituted carbon atom at the chiral center indicated by "*" in formula I, a compound of formula I may exist in, and be isolated in, optically active and racemic forms. If a compound of formula I contains an additional chiral element, such compound of formula I may exist in, and be isolated in, the form of a diastereomeric mixture or as a single diastereomer. It is to be understood that the present invention encompasses a compound of formula I as a mixture of diastereomers, as well as in the form of an individual diastereomer, and that the present invention encompasses a compound of formula I as a mixture of enantiomers, as well as in the form of an individual enantiomer. When R^0 is isopropyl, a compound of formula I may be viewed as an alanyl trifluoromethane derivative. In general, a compound of formula I having the (S)-configuration at the chiral center indicated by "*", which corresponds to the L-alanyl configuration, is preferred. Accordingly, it may be preferred to use the compound of formula I in a form which is characterized as containing, for example, at least 95%, 98% or 99% enantiomeric excess (ee) of the (S)-form. However, owing to the interconvertability of the (S)-isomer and the (R)-isomer by the facile epimerization of the chiral center indicated by "*" in formula I, it may be preferred to utilize a compound of formula I as a mixture of the (S)- and (R)-isomers at the center indicated by "*" in formula I.

As will be appreciated by those skilled in the art, a trifluoromethyl ketone of formula I can exist as a solvate, particularly a hydrate; and such a solvate of a compound of formula I is encompassed by the present invention.

A compound of formula I may exhibit polymorphism. The compound may form solvates in addition to a ketone solvate mentioned above. A compound may exist in more than one tautomeric form. It is to be understood, therefore, that the present invention encompasses any racemic or optically-active form, any polymorphic form, any taut mer or any solvate, or any mixture thereof, which form possesses inhibitory pr perties against HLE, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials)

and how to determine the inhibitory properties against HLE by the standard tests described hereinafter.

It is preferred that the radicals R^0, R, R^5 and R^6 not contain nor introduce an additional element of chirality into the molecule beyond the chiral center indicated by "*" in formula I.

Particular values are listed below for radicals, substituents and ranges for illustration only and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A particular value for R^0 is ethyl or isopropyl.

A particular value for D.W-, taken together, is amino, 2,2,2-trifluoroethylamino or 2,2,2-trifluoroethyl.

A particular value for W is a direct bond or imino.

A particular value for G is (1-3C)alkyl, aryl(1-C)alkyl or heteroaryl(1-2C)alkyl which may bear one or more substituents as defined above for G or a part thereof.

A particular value of (1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, 3-methylbutyl, 1-ethylpropyl, hexyl or 4-methylpentyl. A particular value of (3-6C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl. A particular value for the (1-3C)alkyl portion of (3-6C)cycloalkyl-(1-3C)alkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl is methylene, ethylene or trimethylene. A particular value for aryl is phenyl, indenyl or naphthyl. A particular value for heteroaryl is furyl, imidazolyl, tetrazolyl, pyridyl (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl or quinolinyl (or its N-oxide).
A particular value for lower alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl. A particular value for lower acyloxy is acetoxy. A particular value for lower alkoxy is methoxy, ethoxy, propoxy, isoproxy or t-butoxy. A particular value for halogeno is bromo, chloro or fluoro.

A particular value for COORa is carboxy or methoxycarbonyl. A particular value for NRgCHO is formylamino. A particular value for $NRgCOR^2$ is acetylamino r trifluoroacetylamino. A particular value of $CONRdSO_2R^1$ is N-phenylsulfonylcarbamoyl or N-(4-chlorophenylsulfonyl)-carbamoyl.

A more particular value for R^0 is isopropyl. A more particular value for D is methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, phenyl, benzyl, phenethyl, pyridyl, thienyl, 5-tetrazolyl, thiazolyl, quinolinyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, 2-(pyridyl)ethyl, 2-(thienyl)ethyl or 2-(thiazolyl)ethyl wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group D may bear a substituent selected from hydroxy, methoxy, t-butoxy, acetoxy, pivaloyloxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, 2-(dimethylamino)ethoxycarbonyl, cyano, methylsulfonyl, phenylsulfonyl, N-methylsulfonylcarbamoyl, N-phenylsulfonylcarbamoyl, N-(4-chlorophenylsulfonyl)carbamoyl, methylsulfonylamino, amino, dimethylamino, oxazolidin-2-on-3-yl, acetylamino, trifluoroacetylamino, ureido, methylsulfonyl, sulfamoyl, dimethylphosphoryl or diethylphosphoryl. A more particular value for G is methyl, ethyl, benzyl, phenethyl, pyridyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, or 2-(pyridyl)ethyl, wherein an alkyl carbon may bear an oxo group and wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group G may bear a substituent selected from hydroxy, methoxy, acetoxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, phenylcarbamoyl, pyridylcarbamoyl, methylsulfonylamino, amino, dimethylamino, acetylamino, nicotinoylamino, or trifluoroacetylamino.

A particular value for R is, for example, sulfo, aminosulfonyl, dimethylaminosulfonyl, 2,2,2-trifluoroethylaminosulfonyl, 2,2,2-trifluoroethylsulfonyl, trifluoromethylsulfonyl, methylsulfonyl (which may bear a methoxycarbonyl, carboxy or ethylsulfonyl substituent), methylaminosulfonyl, isopropylamino-sulfonyl, butylsulfonyl, butylaminosulfonyl, tert-butylaminosulfonyl, cyclohexylaminosulfonyl, phenylsulfonyl (in which the phenyl may bear a chloro, nitro, amino, acetylamino, trifluoroacetylamino, methoxy, carboxy, N-(4-chlor phenylsulfonyl)carbamoyl, or methylsulfonylamino substituent at the 3- or 4-position), anilino, pyridylsulfonyl, quinolinylsulfonyl, benzylsulfonyl (in which the phenyl ring may bear a nitro r amino substituent at the 3- or 4-position), pyridylmethyl-

sulfonyl, 2-(pyridyl)ethylsulfonyl or benzylaminosulfonyl.

One particular group of compounds of formula I is one in which R^0 and R have any of the values defined above, R^5 is hydrogen and R^6 is hydrogen.

Another particular group of compounds of formula I is one in which R^0 and R have any of the values defined above, R^5 is benzyl, the phenyl ring of which may bear a 3-fluoro, 4-fluoro, 4-trifluoromethyl, 4-methoxycarbonyl, 3-acetoxy, 3-hydroxy, 3-pivaloyloxy, 4-hydroxy, 4-pivaloyloxy, 3-trifluoroacetylamino or 3-amino substituent, and R^6 is hydrogen.

A further particular group of compounds of formula I is one in which R^0 and R have any of the values defined above, R^5 is hydrogen, and R^6 is 2-furyl, 2-thienyl, 3-pyridyl or phenyl in which the phenyl may bear one or two halogeno, trifluoromethyl, methyl, hydroxy, methoxy, tert-butoxy, methoxycarbonyl or carboxy substituents; and, more particularly, R^6 is phenyl, 4-fluorophenyl or 2-thienyl.

Specific compounds of formula I are described in the accompanying Examples. Of these, compounds of particular interest, along with their pharmaceutically acceptable salts, include those described in Examples 21, 45, 46 and 57.

A pharmaceutically acceptable salt of an acidic compound of formula I is one made with a base which affords a pharmaceutically acceptable cation, which includes alkalai metal salts (especially lithium, sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from appropriate organic bases such as triethylamine, morpholine, piperidine and triethanol amine. A pharmaceutically acceptable salt of a basic compound of formula I includes an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion, including for example, a strong acid such as hydrochloric, sulfuric or phosphoric acid.

A compound of formula I may be made by processes which include processes known in the chemical art for the production of structurally analogous heterocyclic and peptidic c mpounds. Such pr cesses and intermediates for the manufacture f a compound of formula I as defined above are provided as further features of the

invention and are illustrated by the following procedures in which the meanings of generic radicals are as defined above:

(A) Oxidizing a corresponding alcohol of formula II. It will be recognized that protection of the pyridone 3-amino substituent prior to oxidation and removal of the protecting group after oxidation may be required or preferred if the amino group is not stable to the oxidation conditions employed. A convenient method may be the use of excess dimethyl sulfoxide and a water soluble carbodimide, with dichloroacetic acid as a catalyst, in a inert solvent such as toluene at about room temperature, for example as described in Example 1. Other methods which may be useful include the use of alkaline aqueous potassium permanganate solution; the use of oxalyl chloride, dimethyl sulfoxide and a tertiary amine; the use of acetic anhydride and dimethyl sulfoxide; the use of chromium trioxide pyridine complex in methylene chloride; and the use of a hypervalent iodine reagent, such as a periodinane, for example 1,1,1-triacetoxy-2,1-benzoxidol-3(3H)-one with trifluoroacetic acid in dichloromethane.

(B) For a compound of formula I which bears a hydroxy substituent on an aryl or heteroaryl group, cleaving the alkyl ether or acyloxy ester of a corresponding compound of formula I which bears a lower alkoxy or lower acyloxy substituent on an aryl or heteroaryl group. Convenient methods include, for example, the cleavage of a methoxy group using boron tribromide and the cleavage of a t-butoxy group using trifluoroacetic acid for an alkyl ether, and the acidic or alkaline hydrolysis of an acyloxy group.

(C) For a compound of formula I wherein R is 2,2,2-trifluoroethoxycarbonyl or 2,2,2-trifluoroethylaminocarbonyl, acylation of a corresponding amine of formula V with 2,2,2-trifluoroethyl chloroformate or 2,2,2-trifluoroethyl isocyanate. The acylation is conveniently carried out in an inert solvent or diluent, such as dichloromethane, tetrahydrofuran or toluene, at about ambient temperature, using an organic base such as, for example, triethylamine or pyridine, or an inorganic base, such as sodium or potassium carbonate, as an acid acceptor when the chlor f rmate is used. When the is cyanate is used, it may be preferred t use a catalyst, such as f r example, cuprous chloride.

(D) For a compound of formula I wherein R is a sulfonyl group of formula D.W.SO^2-, sulfonylation of a corresponding amine of formula V with a corresponding sulfonic acid of formula D.W.SO_2.OH, or an activated derivative thereof, such as an acid halide, particularly a sulfonyl (or sulfamoyl) chloride of formula D.W.SO_2.Cl. The sulfonylation is conveniently carried out in an inert solvent or diluent, such as dichloromethane, tetrahydrofuran or toluene, at about ambient temperature, using an organic base such as, for example, triethylamine or pyridine, or an inorganic base, such as sodium or potassium carbonate, as an acid acceptor. If a sulfonyl chloride is not commercially available, it may be obtained by a conventional method.

(E) For a compound of formula I wherein R is a group G, substitution of the group X of a corresponding compound of formula G-X, wherein X is a conventional leaving group, such as for example halogeno, methylsulfonyloxy, trifluoromethylsulfonyloxy or diazonium, with a corresponding amine of formula V, optionally using a conventional catalyst.

(F) For a compound of formula I which bears a group of formula COORa in which Ra is hydrogen (a carboxy group), decomposing the ester group of a corresponding ester made with a conveniently removed acid protecting group, for example a corresponding compound of formula I in which Ra is not hydrogen. The decomposition may be carried out using any one of the variety of procedures well known in organic chemistry, for example basic hydrolysis using lithium or sodium hydroxide, or by hydrogenolysis of a benzyl ester.

(G) Removal by using a conventional method of the nitrogen protecting group of a corresponding compound bearing a conventional nitrogen protecting group to afford a corresponding compound of formula I which contains an amino N-H residue; particularly for a compound of formula I wherein R is G, the removal of an activating/protecting group Rx from a corresponding compound of formula Vb. Rx is a group which protects and activates a primary amino group for substitution, such as for example benzyloxycarbonyl or trifluoroacetyl. Conventional methods include, for example, removal of a benzyloxycarbonyl group by hydrogenolysis, removal of a

benzyloxycarbonyl or tert-butoxycarbonyl group by treatment with a strong acid, for example with trifluoromethanesulfonic acid in an inert solvent such as dichloromethane, or basic hydrolysis of a trifluoroacetyl group.

(H) For a compound of formula I bearing a moiety of formula COORa, CH_2COORa, CONRbRc, $CH_2CONRbRc$, $COO(CH_2)_2NReRf$ or $CONRdSO_2R^1$, acylation of a corresponding compound of formula HORa, HNRbRc, $HO(CH2)_2NReRf$ or $HNRdSO_2R^1$ with a corresponding acid of formula I bearing a moiety of formula COORa in which Ra is hydrogen, or an activated derivative thereof.

(I) For a compound of formula I bearing a lower acyloxy group or a group of formula NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCONRiRj or $NRkSO_2R^3$, acylation or sulfonylation of a corresponding compound of formula I bearing a hydroxy group or an amino group of formula NHRg, NHRh or NHRk (i.e. an amino group of formula NReRf is which Re is hydrogen and Rf is Rg, Rh or Rk) with an activated derivative of a corresponding acid of formula HOCHO, $HOCOR^2$, $HOCOOR^2$, HOCONRiRj (including an isocyanate or isothiocyanate) or $HOSO_2R^3$, respectively, using a conventional method.

(J) For a compound of formula I which bears a heteroaryl N-oxide group, oxidation of a corresponding compound of formula I which bears a heteroaryl group using a conventional oxidant, such as for example dioxirane in acetone.

(K) For a compound of formula I which bears a primary amino group, reduction of a corresponding compound bearing a nitro group using a conventional reducing method, such as for example, hydrogenation over a palladium catalyst, or reduction with tin(II) chloride.

Whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of an acidic or basic compound of formula I is required, it may be obtained by reacting the acidic or basic form of such a compound of formula I with a base or acid affording a physiologically acceptable counterion or by any other conventional procedure.

If not commercially available, the necessary starting materials for the above procedures may be made by procedures which are

selected from standard techniques of heterocyclic chemistry and peptide chemistry, techniques which are analogous to the synthesis of known, structurally similar compounds, and techniques which are analogous to the above described procedures or the procedures described in the Examples. For uniformity and clarity, compounds herein are represented as the 2-pyridone, rather than the 2-hydroxypyridine, tautomers.

As will be clear to one skilled in the art, a variety of sequences is available for preparation of the starting materials. According to one of the available routes, a key intermediate pyrid-2-one-3-carboxylic acid of formula III may be prepared as shown in Scheme I (set out, together with other Schemes, folloving Examples) and as described in the Examples. In the Schemes, CBZ represents a benzyloxycarbonyl group.

In general, in a formal sense, a ketone of formula $R^5.CH_2.CO.R^6$ may be formylated, then cyclized with cyanoacetamide to afford a pyrid-2-one-3-carbonitrile of formula IV. As shown in Example 1, part c, (Cyclization Method A) the ketone may be formylated with dimethylformamide dimethyl acetal in acetonitrile then cyclized with cyanoacetamide, using sodium methoxide in dimethylformamide. Alternatively, (Cyclization Method B) the ketone may be formylated using sodium methoxide and ethyl formate in tetrahydrofuran or ether, distilling the solvent, dissolving the resulting salt in water, adding acetic acid to pH 9, and heating with cyanoacetamide at 90 °C to achieve the cyclization. As a further varation, (Cyclization Method C) the salt resulting from formylation with sodium methoxide and ethyl formate, followed by removal of the solvent, may be cyclized with cyanoacetamide by heating an aqueous solution with piperidine acetate as a catalyst. Where more than one product is possible from the cyclization reaction, the product selectivity may be controlled by the cyclization (and formylation) method chosen. For example, cyclization of phenylacetone by Cyclization Method A affords 6-methyl-5-phenyl-pyrid-2-one-3-carbonitrile; but cyclizati n of phenylacetone by Cyclization Method C affords 6-benzylpyrid-2-one-3-carbonitrile. Hydrolysis of the cyano group of a compound of formula IV, for example by heating with 48% hydrobromic acid in acetic acid (Hydrolysis Method

A, Example 1, part d) or with sodium hydroxide solution in a pressure vessel (Hydrolysis Method B) affords a corresponding carboxy derivative of formula III. For a compound in which R^6 is B.Y- and Y is ethylene or trans-vinylene, it may be preferred to proceed via an alternative route to an acid of formula III. Thus, cyclization of a ketone of formula $R^5.CH_2.CO.CH_3$ affords a 6-methyl pyridone derivative of formula IVa, for example, cyclizing acetone by Cyclization Method C. Bis-metallation, followed by alkylation with a reagent of, for example, formula $B.CH_2.Br$ affords a corresponding nitrile of formula IV in which Y is ethylene. Alternatively, bis-metallation of a 6-methyl pyridone of formula IVa, followed by condensation with an aldehyde of formula B.CHO, affords a pyrid-2-one-3-carbonitrile of formula IVb which may be converted by acid hydrolysis and dehydration into a corresponding pyride-2-one-3-carboxylic acid of formula III in which Y is trans-vinylene.

An acid of formula III may be converted into a corresponding isocyanate of formula VI by a conventional method, for example by using diphenylphosphoryl azide in an inert solvent, as described in Example 1, part e. Conveniently, the isocyanate is not isolated, but is converted into a benzyl urethane of formula VII as also is shown in Scheme I. (An isocyanate of formula VI may undergo intramolecular cyclization to the oxygen at the pyridone 2-position, thereby forming a corresponding cyclic carbamate, which carbamate similarly may afford a corresponding compound of formula VII.)

Elaboration of a substituted amino pyridone of formula VII into a corresponding intermediate alcohol of formula II or a corresponding intermediate amine of formula V or protected amine formula Vb may be carried out as outlined in Scheme II. Alkylation of a compound of formula VII with an iodoacetamide derivative, for example as described in Example 1, part f, for a compound in which R^0 is isopropyl, affords a 1-substituted pyridone of formula VIII, wherein Rp represents an alcohol protecting group, conveniently tert-butyldimethylsilyl. (The corresponding 2-alkoxypyridine resulting from O-alkylation is also obtained. When R^6 is subject to hindered rotation, for example when R^5 is methyl and R^6 is phenyl, or, for example, when R^5 is hydrogen and R^6 is 2-chlorophenyl as in

Example 1, the ratio of N-alkylated product to O-alkylated product is increased.) The benzyloxycarbonyl group of a compound of formula VIII may be removed by a conventional method, for example by hydrogenolysis as described in Example 1, part g, to afford a corresponding 3-amino pyridone of formula IX. (In Example 1, the hydrogenolysis of a 2-chloro group of the phenyl substituent is also described.)

For a compound of formula X wherein R is 2,2,2-trifluoro-ethoxy carbonyl or 2,2,2-trifluoroethylaminocarbonyl, a 3-amino pyridone of formula IX may be acylated by using a method similar to one described above in process (C) to afford a corresponding pyridone of formula X. For a compound of formula X wherein R is a sulfonyl group of formula $D.W.SO^2-$, a 3-amino pyridone of formula IX may be sulfonylated by using a convention method to afford a corresponding pyridone of formula X. Conventional sulfonylation methods include those described above in process (D) for the sulfonylation of an amine of formula V. (Should a portion of bis-sulfonylated product be obtained, treatment with aqueous base at an elevated temperature may be used to remove the more labile second sulfonyl group at a convenient stage in the synthesis; see for example Example 6, parts a.-b.) For a compound of formula X wherein R is a group G, a 3-amino pyridone of formula IX may be subjected to a conventional substitution reaction similar to one described above in process (E) to afford a corresponding pyridone of formula X.

Removal of a tert-butyldimethylsilyl group from a compound of formula X in which Rp is tert-butyldimethylsilyl to provide a corresponding alcohol of formula II may be carried out using tetrabutylammonium fluoride in an inert solvent; it may be preferred to use acetic acid to buffer the reaction conditions.

An alternative order of steps to convert a protected compound of formula VIII into a corresponding alcohol of formula II can be used as well. Thus, removal of the alcohol protecting group of a compound of formula VIII affords the corresponding alcohol of formula VIIIa. Deprotection of the amino group of a compound of formula VIIIa affords a corresponding amino alc hol of formula XXVII (see Scheme IV for formula XXVII) which can be converted into a corresponding alcohol of formula II using a conventional procedure.

A different route which obviates the need for an alcohol deprotection step is also shown in Scheme II. Thus, a pyridone of formula VII may be alkylated, for example with ethyl or t-butyl iodoacetate, to afford a corresponding ester of formula XI, wherein Rq is a conveniently removable acid protecting group, for example ethyl or t-butyl. Removal of the acid protecting group of an ester of formula XI by a conventional method, for example by base catalyzed hydrolysis or by acid catalyzed elimination, affords a corresponding acid of formula XII. An acid of formula XII may be coupled with the requisite amino alcohol for example, with 3-amino-1,1,1-trifluoro-4-methyl-2-pentanol, for example as described in Example 7, part g, to afford a corresponding alcohol of formula VIIIa.

An alternative route for the preparation of an intermediate acid of formula XII, beginning with a ketone of formula $R^5.CH_2.CO.R^6$ and involving a novel pyridone synthesis, which may be a preferred route, is described in Example 7, parts a.-f., for the conversion of acetophenone into 3-benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridylacetic acid. The coupling to provide the corresponding alcohol of formula VIIIa, 2-(3-benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-2-hydroxy-1-isopropyl-propyl)acetamide, is also described in Example 7.g., as noted above.

Oxidation of an alcohol of formula VIIIa, using a method similar to one described in process (A) for oxidation of an alcohol of formula II, affords a corresponding ketone of formula VIIIb. Removal of the nitrogen protecting group of a ketone of formula VIIIb by hydrogenolysis or by treatment with a strong acid, for example as described in Example 7.i., affords a corresponding starting material amine of formula V.

A preferred method for introducing the substituent R when it is a group G, particularly when it is an alkyl or substituted alkyl group, is by the use of a corresponding compound in which the pyridone 3-amino substituent bears an activating/protecting group of formula Rx, for example, benzyloxycarbonyl or trifluoroacetyl. Thus, acylation of a compound of formula V with triflu roacetic anhydride affords a corresponding compound of formula Va in which Rx is trifluoroacetyl, which compound may be prepared by an alternative

order of steps via the corresponding compound of formula IX and 3-trifluoroacetylaminopyridones analogous to compounds of formulae VIII and VIIIa. It will be noted that a compound of formula VIIIb is, itself, a corresponding compound of formula Va in which Rx is benzyloxycarbonyl. Alkylation, using a corresponding reagent of formula G.X in which G is alkyl or substituted alkyl, then provides a corresponding intermediate of formula Vb, for example as described in Example 53.a.

Synthesis routes involving a cross coupling reaction to introduce a substituent R^5 into intermediate compounds are outlined in Scheme III. These routes may be preferred when R^5 has the value B.Y- and Y is methylene, ethylene or trans-vinylene. Thus, a pyridone of formula VII in which R^5 is hydrogen may be converted into a corresponding 5-iodo pyridone of formula XXI by treatment with an iodinating agent, for example N-iodosuccinimide. An appropriate halide, for example a bromide of formula $B.CH_2.Br$, may be converted into a corresponding organozinc reagent, for example $B.CH_2.Zn.Br$, by treatment with zinc dust in tetrahydrofuran, and cross-coupled with an iodide of formula XXI using a palladium catalyst, such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) to afford a corresponding compound of formula VII in which R^5 is B.Y- and Y is methylene. A similar cross coupling utilizing a bromide of formula B.Y.Br in which Y is trans-vinylene may be useful to convert an iodide of formula XXI into a corresponding compound of formula VII in which R^5 is B.Y- and Y is trans-vinylene. At a convenient point in a synthesis, a compound in which R^5 is B.Y- and Y is trans-vinylene may be hydrogenated to afford a corresponding compound in which R^5 is B.Y- and Y is ethylene.

Alternatively, an iodide of formula XXI may be alkylated to afford a corresponding iodide of formula XXII or XXIII which may be further cross coupled as described above to provide a corresponding compound of formula VIII or XI.

Alternative synthesis routes in which a 3-nitro pyridone serves as a precursor to a 3-amino pyridone are outlined in Scheme IV. They may be particularly useful when the 3-nitro derivative is readily available, such as when R^5 and R^6 are hydrogen. Alternatively,

beginning with a ketone of formula $R^5.CH_2.CO.R^6$, the corresponding 3-nitropyridone may be prepared in a manner analogous to Cyclization Method A by heating a dimethylformamide solution of the ammonium salt of nitroacetamide (prepared according to J. Org. Chem. (1958), 23, 113-114) with the product isolated from treatment of the ketone with dimethylformamide dimethyl acetal in acetonitrile.

Direct reduction of the nitro group, followed by protection of the amine obtained with a benzyloxycarbonyl group provides a pyridone of formula VII, which may be converted into a corresponding intermediate of formula II, V or Vb using a route outlined in Scheme II. Alternatively, for a compound in which R is an acyl or sulfonyl group, direct reduction of the nitro group may be followed by acylation or sulfonylation of the amine obtained to provide a pyridone of formula VIIb, which may be converted into a corresponding intermediate of formula II using a route similar to one outlined in Scheme II for a compound of formula VII.

Using a different order of steps, the 3-nitro pyridone may be alkylated first to provide an ester of formula XXIV. The ester of formula XXIV may be converted into the corresponding acid of formula XXV. The acid of formula XXV also may be obtained by allylation of the starting 3-nitro pyridone, followed by oxidative cleavage of the 1-allyl group using potassium permanganate. By coupling with the appropriate amino alcohol, an acid of formula XXV may be converted into a nitro alcohol of formula XXVI. A nitro alcohol of formula XXVI may be reduced to afford a corresponding 3-amino pyridone of formula XXVII which may be converted into a corresponding intermediate alcohol of formula II using one of the methods described above. In addition, a nitro alcohol of formula XXVI may be oxidized to a corresponding nitro ketone of formula XXVIII. Reduction of the nitro group of a nitro ketone of formula XXVIII affords an intermediate amine of formula V.

An analogous route from a nitro compound of formula XXIV involves first reducing the nitro group to afford a corresponding amino c mpound of f rmula XXIX. Protection f a compound of formula XXIX with a benzyloxycarbonyl group affords a compound of formula XI, which may be further converted into a corresp nding compound of

formula II, V or Vb using a method described in Scheme II. Alternatively, for a compound in which R is an acyl or sulfonyl group, acylation or sulfonylation of a compound of formula XXIX affords a compound of formula XIb, which may be further converted into a corresponding compound of formula II using a similar method to that described in Scheme II for a compound of formula XI, that is, conversion into a corresponding acid of formula XIIb, followed by coupling with a requisite amino alcohol.

For a compound in which R is is a group G, it will be clear that the methodology described above using an activating/protecting group of formula Rx to introduce the substituent R on the pyridone 3-amino group may be utilized analogously at any convenient stage of a synthetic scheme.

The trifluoromethyl amino alcohols required for the synthesis routes described above may be prepared by known routes. For example, 3-amino-1,1,1-trifluoro-4-methyl-2-pentanol (as its hydrochloride salt) conveniently may be obtained as described in U.S. Patent 4,910,190 in Example 4 (as a single diastereomer) or Example 6 (as a single enantiomer of a single diastereomer). If it is desired to carry out a chiral synthesis of a compound of formula I, using the single enantiomer in a substantially enantiomerically pure form and using methods and conditions which avoid epimerization at the center indicated by "*" in formula I provide such a synthesis.

It may be desired optionally to use a protecting group during all or portions of the above described processes; the protecting group then may be removed when the final compound or a required starting material is to be formed. As will be clear to one skilled in the art, the order of steps in the sequences leading to the starting materials and products of the invention may be altered if appropriate considerations relative to coupling methods, racemization, deprotection methods, etc. are followed.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred t as a "Compound") may be demonstrated by standard tests and clinical studies, including those described below.

Inhibition Measurements:

The potency of a Compound to act as an inhibitor of human leukocyte elastase (HLE) on the low molecular weight peptide substrate methoxy-succinyl-alanyl-alanyl-prolyl-valine-p-nitroanilide is determined as described in U.S. Patent 4,910,190. The potency of an inhibitor is evaluated by obtaining a kinetic determination of the dissociation constant, K_i, of the complex formed from the interaction of the inhibitor with HLE. If a Compound is found to be a "slow-binding" inhibitor of HLE, special methods of analysis to accurately determine K_i values for the inhibition of HLE are carried out as described in U.S. Patent 4,910,190. In general, the K_i values for Compounds of the invention which were tested are generally on the order of 10^{-7} M or much less.

Acute Lung Injury Model:

Animal models of emphysema include intratracheal (i.t.) administration of an elastolytic protease to cause a slowly progressive, destructive lesion of the lung. These lesions are normally evaluated a few weeks to a few months after the initial insult. However, these proteases also induce a lesion that is evident in the first few hours. The early lesion is first hemorrhagic, progresses to an inflammatory lesion by the end of the first 24 hours and resolves in the first week post insult. To take advantage of this early lesion, the following model (described in Williams, et al., American Review of Respiratory Diseases (1991), 144, 875-883) was used.

Hamsters are first lightly anesthetized with Brevital. Phosphate buffered saline (PBS) pH 7.4, either alone or containing human leukocyte elastase (HLE), is then administered directly into the trachea. Twenty-four hours later the animals are killed and the lungs removed and carefully trimmed of extraneous tissue. Following determination of wet lung weight, the lungs are lavaged with PBS and total lavagable red and white cells recovered are determined. The values for wet lung weights, total lavagable red cells and total lavagable white cells are elevated in a dose-dependent manner following administration of HLE. Compounds that are effective elastase inhibitors can prevent or diminish the severity of the enzyme-induced lesion resulting in lower wet lung weight and reduced

values for total lavagable cells, both red and white, relative to administration of HLE alone. Compounds can be evaluated by administering them intratracheally as solutions or suspensions in PBS, either with or at various times prior to the HLE challenge (400 µg), or by dosing them intravenously or orally as solutions at various times prior to the HLE challenge (100 µg) to determine their utility in preventing an HLE lesion. A solution of a Compound is conveniently prepared using 10% polyethylene glycol 400/PBS or 10% polyethylene glycol 400/water. For a Compound which is acidic or basic, base (e.g. sodium hydroxide solution) or acid (e.g. hydrochloric acid) may be added as indicated to achieve solution. Compounds of this invention produced statistically significant reductions in wet lung weight and total lavagable cells relative to HLE alone.

Acute Hemorrhagic Assay:

This assay relies on monitoring only the amount of hemorrhage in the lung following intratracheal administration of human neutrophil elastase (HNE). Hemorrhage is quantified by disrupting erythrocytes recovered in lung lavage fluid and comparing that to dilutions of whole hamster blood. The screening protocol, similar to that described in Fletcher et al., American Review of Respiratory Disease (1990), 141, 672-677, is as follows. Compounds demonstrated to be HNE inhibitors in vitro are conveniently prepared for dosing as described above for the Acute Lung Injury Model. The compounds are then dosed by mouth to male Syrian hamsters at a fixed time, such as 30 or 90 min, prior to intratracheal administration of 50 µg/animal of HNE in 300 µL phosphate buffered saline (PBS) pH 7.4. Four hours after enzyme administration, the animals are killed with an overdose of pentobarbital sodium, the thorax opened and the lungs and trachea removed. The excised lungs are lavaged with three changes of 2 mL normal saline via a tracheal cannula. The recovered lavages are pooled, the volumes (about 5 mL) are recorded and the lavages stored at 4 °C until assayed. For calculation of the amount of blood in each sample, the thawed lavages and a sample of whole hamster blood are sonicated to disrupt erythrocytes and appropriately diluted into individual wells of a 96-well microtiter plate. The optical densities (OD) of the disrupted lavages and blood samples are determined at 405

nm. The (µL blood equivalents) / (mL lavage) are determined by comparing the OD of the test samples with the OD of the standard curve prepared from whole hamster blood. The total µL equivalents of blood recovered is determined by multiplying recovered lavage volume by the (µL blood equivalents) / (mL lavage) for each sample. Results are reported as % inhibition of hemorrhage with respect to PBS treated controls when the test compound is given at a specified dose and time prior to administration of HNE.

No overt toxicity was observed when Compounds of the invention were administered in the above in vivo tests.

It will be appreciated that the implications of a Compound's activity in the Acute Lung Injury Model or Acute Hemorrhagic Assay are not limited to emphysema, but, rather, that the test provides evidence of general in vivo inhibition of HLE.

Compounds of the present invention which were tested exhibited activity in at least one of the tests described above under Inhibition Measurement, Acute Lung Injury Model and Acute Hemorrhagic Assay. It should be noted that, as would be expected in comparison of in vitro and in vivo results, there was not always a direct correlation between the activities of the compounds measured as K_i values in the Inhibition Measurement test and the reduced values for total lavagable cells and wet lung weights relative to the administration of HLE alone obtained in the Acute Lung Injury Model test or inhibition of hemorrhage in the Acute Hemorragic Assay.

According to a further feature of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a Compound and a pharmaceutically acceptable diluent or carrier. As noted above, another feature of the invention is a method of using a Compound of the invention in the treatment of a disease or condition in a mammal, especially a human, in which HLE is implicated.

A Compound of the present invention may be administered to a warm-bl oded animal, particularly a human, in need thereof for treatment of a disease in which HLE is implicated, in the form f a conventional pharmaceutical composition, for example as generally disclosed in U.S. Patent 4,910,190. The preferred mode of

administration may be via a powdered or liquid aerosol. In a powdered aerosol, a Compound of the invention may be administered in the same manner as cromolyn sodium via a 'Spinhaler' (a trademark) turbo-inhaler device obtained from Fisons Corp. of Bedford, Massachusets at a rate of about 0.1 to 50 mg per capsule, 1 to 8 capsules being administered daily for an average human. Each capsule to be used in the turbo-inhaler contains the required amount of a Compound of the invention with the remainder of the 20 mg capsule being a pharmaceutically acceptable carrier such as lactose. In a liquid aerosol, a Compound of the invention may be administered using a nebulizer such as, for example, a 'Retec' (trademark) nebulizer, in which the solution is nebulized with compressed air. The aerosol may be administered, for example, at the rate of one to about eight times per day as follows: A nebulizer is filled with a solution of a Compound, for example 3.5 mL of solution containing 10 mg/mL; the solution in the nebulizer is nebulized with compressed air; and the patient breathes normally (tidal volume) for eight minutes with the nebulizer in his mouth.

Alternatively, the mode of adminstration may be oral or parenteral, including subcutaneous deposit by means of an osmotic pump. A compound of the invention may be conventionally formulated in an oral or parenteral dosage form by compounding about 10 to 250 mg per unit of dosage with conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted pharmaceutical practice, e.g. as described in U.S. Patent 3,755,340. For parenteral administration, a 1 to 10 mL intravenous, intramuscular or subcutaneous injection would be given containing about 0.02 mg to 10 mg/kg of body weight of a compound of the invention 3 or 4 times daily. The injection would contain a compound of the invention in an aqueous isotonic sterile solution or suspension optionally with a preservative such as phenol or a solubilizing agent such as ethylenediaminetetraacetic acid (EDTA).

For parenteral administration or use in an aerosol, an 10 mg/mL aqueous formulation of an acidic Compound may be prepared, for example by dissolving the Compound (10 mg), dibasic sodium phosphate heptahydrate, USP (11.97 mg), monobasic sodium phosphate, USP

(0.74 mg), sodium chloride, USP (4.50 mg) and sufficient 1 N sodium hydroxide solution or 0.05 M monobasic sodium phosphate solution to achieve pH 7.0-7.5 in sufficient water for injection, USP to afford 1.0 mL (1.01 g), followed by aseptic filtration, and sterile storage using standard procedures.

In general, a Compound of the invention will be administered to humans at a daily dose in the range of, for example, 5 to 100 mg of the Compound by aerosol or 50 to 1000 mg intravenously, or a combination of the two. However, it readily will be understood that it may be necessary to vary the dose of the Compound adminstered in accordance with well known medical practice to take account of the nature and severity of the disease under treatment, concurrent therapy, and the age, weight and sex of the patient receiving treatment. It similarly will be understood that generally equivalent amounts of a pharmaceutically acceptable salt of the Compound also may be used. Protocols for the administration of an HLE inhibitor and evaluation of the patients are described in the European Patent Applications with Publication Numbers 458535, 458536, 458537, and 463811 for the treatment or prevention of cystic fibrosis, ARDS, bronchitis, and hemorrhage associated with acute non-lymphocytic leukemia or its therapy, respectively; and a Compound of the invention may be used similarly for the treatment of those diseases and conditions either alone or in combination with another therapeutic agent customarily indicated for the treatment of the particular condition. For therapeutic or prophylactic treatment of a vascular disease or related condition in a mammal in which neutrophils are involved or implicated, a Compound of the invention may conveniently be administered by a parenteral route, either alone or simultaneously or sequentially with other therapeutically active agents customarily administered for the condition.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); perations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;

(ii) organic solutions were dried over anhydrous sodium

sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 °C;

(iii) chromatography means 'flash chromatography' (method of Still) carried out on Merck Kieselgel (Art 9385 from E. Merck, Darmstadt, Germany); if "acidic silica gel" is indicated, material custom prepared by J. T. Baker Chemical Co., Phillipsburg, NJ, USA, and having a pH of about 6 when slurried in water was used; reversed phase chromatography means flash chromatography over octadecylsilane (ODS) coated support having a particle diameter of 32-74 μ, know as "PREP-40-ODS" (Art 731740-100 from Bodman Chemicals, Aston, PA, USA); thin layer chromatography (TLC) was carried out on 0.25 mm silica gel GHLF plates (Art 21521 from Analtech, Newark, DE, USA); reversed phase-TLC (RP-TLC) was carried out Whatman $MKC_{18}F$ plates (Art 4803-110 from Bodman Chemicals);

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(vi) final products had satisfactory nuclear magnetic resonance (NMR) spectra;

(vii) yields are given for illustration only and are not necessarily those which may be obtained by diligent process development; preparations were repeated if more material was required;

(viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 250 MHz using DMSO-d_6 (or DMSO-d_6/D_2O, indicated herein as DMSO/D_2O) as solvent; conventional abbreviations for signal shape are used; for AB spectra the directly observed shifts are reported;

(ix) chemical symbols have their usual meanings; SI units and symbols are used;

(x) reduced pressures are given as absolute pressures in pascals (Pa); elevated pressures are given as gauge pressures in bars;

(xi) solvent ratios are given in volume:volume (v/v) terms; and

(xii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionizaton mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI) or fast atom bombardment (FAB); generally, only peaks which indicate the parent mass are reported.

EXAMPLES 1-6

The following compounds of Formula I wherein R^0 is isopropyl, R^5 is hydrogen, R^6 is phenyl and R is the indicated value were prepared by oxidation of the corresponding alcohols of formula II using a procedure similar to that which follows:

To a solution of an alcohol of Formula II wherein R^0 is isopropyl, R^5 is hydrogen, R^6 is phenyl and R is the indicated value (0.2 millimolar in dimethylsulfoxide:toluene, 1:1) is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10 equivalents) and dichloroacetic acid (5 equivalents). After overnight stirring, the reaction mixture is diluted with ethyl acetate; washed (10% hydrochloric acid, saturated aqueous sodium bicarbonate, brine), dried and evaporated to give material which is purified using chromatography, eluting with the indicated solvent, except as otherwise noted, to provide the product.

Example 1: R=benzylsulfonyl: Chromatography solvent: dichloromethane:ethyl acetate (95:5), and drying overnight in a vacuum oven; mp 192-193 °C; TLC: R_f=0.29, methanol:dichloromethane (5:95); NMR: 0.85 (d,3), 0.90 (d,3), 2.14 (m,1), 4.57 (m,5), 6.10 (d,1), 7.24 (d,1), 7.36 (m,10), 8.74 (d,1), 8.82 (s,1); MS: m/z=550(M+1).
Analysis for $C_{26}H_{26}F_3N_3O_5$:
Calculated: C, 56.82; H, 4.77; N, 7.65
Found: C, 56.46; H, 5.03; N, 7.50

Example 2: R=2-(2-pyridyl)ethylsulfonyl: Chromatography solvent: methanol:dichloromethane (2:98), followed by trituration with methyl tert-butyl ether; mp 80-86 °C; TLC: R_f=0.43, methanol:dichloromethane (5:95); NMR: 0.76 (d,3), 0.84 (d,3), 2.21 (m,1), 3.24 (t,2), 3.83 (t,2), 4.44 (d,1), 4.58 (d,1), 6.25 (d,1), 7.46 (m,7), 7.74 (dd,1), 8.48 (d,1), 8.73 (d,1), 9.13 (s,1); MS: m/z=565(M+1).

Analysis for $C_{26}H_{27}N_4O_5S \cdot 0.3$ methyl tert-butyl ether:
Calculated: C, 54.88; H, 5.33; N, 9.31
Found: C, 54.78; H, 5.41; N, 8.94

Example 3: R=8-quinolylsulfonyl: Chromatography solvent: dichloromethane:tetrahydrofuran (20:1); TLC: R_f=0.39, dichloromethane:methanol (5:1); MS: m/z=587(M+1).
Analysis for $C_{28}H_{25}F_3N_4O_5S \cdot 1.0\ H_2O$:
Calculated: C, 55.62; H, 4.50; N, 9.43
Found: C, 55.97; H, 4.46; N, 9.15

Example 4: R=butylsulfonyl: Chromatography solvent: dichloromethane:methanol (95:5); TLC: R_f=0.45, dichloromethane:-methanol (20:1); MS: m/z=516(M+1).
Analysis for $C_{23}H_{28}F_3N_3O_5S \cdot 0.25\ H_2O$:
Calculated: C, 53.12; H, 5.52; N, 8.08
Found: C, 53.17; H, 5.64; N, 8.01

Example 5: R=4-nitrobenzylsulfonyl: Chromatography solvent: dichloromethane:methanol (gradient, 100:0, 99:1, 98:2); TLC: R_f=0.45, dichloromethane:methanol (95:5); MS: m/z=595 (M+1).
Analysis for $C_{26}H_{25}F_3N_4O_7S$:
Calculated: C, 52.52; H, 4.24; N, 9.42
Found: C, 52.17; H, 4.27; N, 9.49

Example 6: R=3-pyridylsulfonyl: Purified by chromatography, with methanol:dichloromethane (2:98) as the eluent for three columns and ethyl acetate:hexane (3:1) as the eluent for a fourth column; TLC: R_f=0.35, ethyl acetate:hexane (3:1); MS: m/z=537(M+1).
Analysis for $C_{24}H_{23}F_3N_4O_5S \cdot 1.5\ H_2O$:
Calculated: C, 51.15; H, 4.65; N, 9.94
Found: C, 51.18; H, 4.59; N, 9.37

The intermediate alcohols of Formula II used in Examples 1-6 were prepared as follows.

EXAMPLES 1.a.-6.a.

tert-Butyldimethylsilyl ethers of the alcohols of Formula II wherein R^0 is isopropyl, R^5 is hydrogen, R^6 is phenyl and R is the indicated value were prepared using the following general procedure:

2-(3-Amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(2-tert-butyldimethylsilyloxy-3,3,3-trifluoro-1-isopropylpropyl)acetamide is sulfonylated, using triethylamine and the required sulfonyl chloride in tetrahydrofuran. The solution is stirred overnight, diluted with ethyl acetate, washed (10 % hydrochloric acid, saturated aqueous sodium bicarbonate, brine), dried and evaporated to give the sulfonamide, which is purified using chromatography, eluting with the indicated solvent, except as otherwise noted.

Example 1.a.: R=benzylsulfonyl: The product was used without additional purification; TLC: R_f=0.82, toluene:ethyl acetate (2:1); MS: m/z=666(M+1).

Example 2.a.: R=2-(2-pyridyl)ethylsulfonyl: The product was used without additional purification; TLC: R_f=0.42, toluene:ethyl acetate (1:1); MS: m/z=681(M+1).

Example 3.a.: R= 8-quinolylsulfonyl: Chromatography solvent: dichloromethane:methanol (25:1); TLC: R_f=0.51, dichloromethane:methanol (20:1); MS: m/z=731(M+1).

Example 4.a.: R=butylsulfonyl; The product was used without additional purification; TLC: R_f=0.68, toluene:ethyl acetate (2:1); MS: m/z=632(M+1).

Example 5.a.: R=4-nitrobenzylsulfonyl: Pyridine was used in place of triethylamine and the product was used without additional purification; TLC: R_f=0.63, dichloromethane:ethyl acetate (70:30); MS: m/z=711(M+1).

Example 6.a.: R=3-pyridylsulfonyl: Using dichloromethane in place of tetrahydrofuran and using the hydrochloride of 3-pyridylsulfonyl chloride, with two equivalents of base employed. The resulting material was a mixture of mono- and bis-sulfonylation products. The mixture was used directly in Example 6.b.

The required sulfonyl chloride for Example 6.a. was prepared by a method similar to that described by T.F. Mich, in U.S. Patent 4,315,014, for the preparation of 2-(4-pyridyl)ethylsulfonyl chloride hydrochloride: Purified by trituration with carbon tetrachloride, acetonitrile, and diethyl ether.

EXAMPLES 1.b.-6.b.

The alcohols of Formula II wherein R^0 is isopropyl, R^5 is hydrogen, R^6 is phenyl and R is the indicated value were prepared using the following general procedure (acetic acid buffered fluoride):

The corresponding tert-butyldimethylsilyl ether prepared in Examples 1.a.-6.a. is dissolved in tetrahydrofuran and treated with tetrabutylammonium fluoride (1 M in tetrahydrofuran, 1.1 equivalents) and glacial acetic acid (1 equivalent). The mixture is stirred for 4.5 hours, diluted with ethyl acetate, washed (water, brine), dried and evaporated to give the product, which is used without further purification, except as otherwise noted.

Example 1.b.: R=benzylsulfonyl: TLC: R_f=0.31, toluene:ethyl acetate (2:1); MS: m/z=552(M+1).

Example 2.b.: R=2-(2-pyridyl)ethylsulfonyl: Chromatographed, eluting with methanol:dichloromethane (3:97), followed by trituration with hexane; TLC: R_f=0.33, methanol:dichloromethane (5:95); MS: m/z=567(M+1).

Example 3.b.: R=8-quinolylsulfonyl: TLC: R_f=0.16, dichloromethane:methanol (20:1); MS: m/z=589(M+1).

Example 4.b.: R=butylsulfonyl: Chromatographed, eluting with dichloromethane:methanol (98:2); TLC: R_f=0.5, dichloromethane:-methanol (95:5); MS: m/z=518(M+1).

Example 5.b.: R=4-nitrobenzylsulfonyl: TLC: R_f=0.51, dichloromethane:-ethyl acetate (70:30); MS: m/z=597(M+1).

Example 6.b.: R=3-pyridylsulfonyl: The product was a a mixture of mono- and bis-sulfonyl compounds. The mixture was dissolved in tetrahydrofuran and treated with 1 N NaOH at 60 °C for 1.5 hours. Ethyl acetate was added followed by 1 N hydrochloric acid to pH 2. The mixture was diluted with water and the organic layer was dried ($MgSO_4$), evaporated and purified by chromatography, with methanol:dichloromethane (3:97) as the eluent, to give the mono-sulfonyl compound; TLC: R_f=0.40, methanol:dichloromethane (10:90); MS: m/z=539(M+1).

The intermediate 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(2-tert-butyldimethylsilyloxy-3,3,3-trifluoro-1-isopropylpropyl)acetamide used in Examples 1.a.-6.a. was prepared as described at Example 22.a.-22.e. of European Patent Application, Publication Number 509769; see also preparations described at Example 1.a.-1.h. and Example 14.a. of that application.

EXAMPLE 7

2-(3-Methoxycarbonylmethylsulfonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

To a solution of 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide (0.50 g) in tetrahydrofuran (6 mL), cooled to 0 °C, was added, dropwise, methyl chlorosulfonylacetate (0.29 g). Immediately, triethylamine (0.38 g) was added dropwise to the reaction mixture, generating a color change from light orange to green. After 10 min stirring, the reaction mixture was diluted with 25 mL ethyl acetate and acidified with 1 N

aqueous hydrochloric acid. The organic phase was washed (water, brine), dried (magnesium sulfate) and evaporated to yield 0.60 g of an orange foam. Chromatography, using acidic silica gel and eluant of methylene chloride:tetrahydrofuran (20:1), followed by overnight vacuum-drying (40 °C, 27 Pa), yielded a light-yellow foam (0.35 g); mp 165-168 °C; TLC: R_f=0.33, dichloromethane:tetrahydrofuran (9:1, trace acetic acid); NMR: 0.90 (2d,6), 2.20 (m,1), 3.70 (s,3), 4.4-4.6 (s and m, 4), 4.65 (t,1), 6.20 (d,1), 7.45 (m,6), 8.75 (d,1), 9.35 (s,1); MS: m/z=532(M+1).

Analysis for $C_{22}H_{24}F_3N_3O_7S$:

Calculated: C, 49.72; H, 4.55; N, 7.91

Found: C, 50.55; H, 4.79; N, 7.55

The intermediate 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide may be prepared as dexcribed in European Patent Application, Publication Number 509769 at Example 49 (and the subparts thereunder); see also Example 22.a.-22.b. and Example 167 of that application.

EXAMPLES 8-12

Using a procedure similar to that described in Example 7, the following compounds of Formula I wherein R^0 is isopropyl, R^5 is hydrogen, R^6 is phenyl and R has the indicated value were prepared by sulfonylation of 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide with the corresponding sulfonyl chloride. Except as otherwise noted, the product was purified by chromatography over silica gel.

Example 8: R=methylsulfonyl: Chromatography on acidic silica gel, with dichloromethane:tetrahydrofuran (20:1) as the eluent; TLC: R_f=0.37, dichloromethane:tetrahydrofuran (9:1, with 2.5% acetic acid); 300 MHz NMR: 0.90 (2d,6), 2.15 (m,1), 3.10 (s,3), 4.50 (q,2), 4.63 (t,1), 6.20 (d,1), 7.40 (m,6), 8.75 (d,1), 8.95 (s,1); MS: m/z=471(M+1).

Analysis for $C_{20}H_{22}F_3N_3O_5S$:

Calculated: C, 50.74; H, 4.68; N, 8.88
Found: C, 51.25; H, 4.89; N, 8.48

Example 9: R=methylsulfonylmethylsulfonyl: Purified by trituration with ethyl acetate; TLC: R_f=0.2, methanol:dichloromethane (5:95); 300 MHz NMR: 0.84 (d,3), 0.89 (d,3), 2.15 (m,1), 3.22 (s,3), 4.48 (q,2), 4.64 (t,1), 5.36 (s,2), 6.23 (d,1), 7.41 (m,6), 8.75 (d,1), 9.71 (s,1); MS: m/z=552(M+1).
Analysis for $C_{21}H_{24}F_3N_3O_7S_2$:
Calculated: C, 45.73; H, 4.38; N, 7.62
Found: C, 45.41; H, 4.40; N, 7.59

Example 10: R=aminosulfonyl: Recrystallized from hexane:ethyl acetate (1:10); TLC: R_f=0.22, dichloromethane:methanol (20:1); MS: m/z=475(M+1).
Analysis for $C_{19}H_{21}F_3N_4O_5S \cdot 0.25\ H_2O$:
Calculated: C, 47.65; H, 4.52; N, 11.70
Found: C, 47.73; H, 4.46; N, 11.60

Example 11: R=benzylaminosulfonyl: Purified by trituration with diethyl ether; TLC: R_f=0.26, dichloromethane:methanol (20:1); MS: m/z=565(M+1).
Analysis for $C_{26}H_{27}F_3N_4O_5S \cdot 0.25\ H_2O$:
Calculated: C, 55.31; H, 4.82; N, 9.92
Found: C, 54.91; H, 4.88; N, 9.74

Example 12: R=trifluoromethylsulfonyl: Chromatography solvent: dichloromethane:methanol (40:1); TLC: R_f=0.17, dichloromethane:methanol (20:1); MS: m/z=528(M+1).
Analysis for $C_{20}H_{19}F_6N_3O_5S$:
Calculated: C, 45.54; H, 3.63; N, 7.97
Found: C, 45.49; H, 3.68; N,7.76

EXAMPLES 13-25

Using a procedure similar to that described in Example 7, except replacing triethylamine with pyridine, the following compounds of Formula I wherein R^0 is isopropyl, R^5 is hydrogen, R^6 is phenyl and R has the indicated value were prepared by sulfonylation of 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide with the corresponding sulfonyl chloride and purified by chromatography over silica gel, except as otherwise indicated. If the sulfonyl chloride was a pyridine hydrochloride, an extra equivalent of base was used.

Example 13: R=phenylsulfonyl: Chromatography solvent: dichloromethane:tetrahydrofuran (20:1); TLC: R_f=0.31, dichloromethane:methanol (20:1); MS: m/z=536(M+1).
Analysis for $C_{25}H_{24}F_3N_3O_5S$:
Calculated: C, 56.07; H, 4.52; N, 7.85
Found: C, 55.82; H, 4.66; N, 7.58

Example 14: R=4-chlorophenylsulfonyl: Chromatography solvent: dichloromethane:tetrahydrofuran (20:1); TLC: R_f=0.30, dichloromethane:methanol (20:1); MS: m/z=570(M+1).
Analysis for $C_{25}H_{23}ClF_3N_3O_5S$:
Calculated: C, 52.68; H, 4.07; N, 7.37
Found: C, 52.71; H, 4.25; N, 7.12

Example 15: R=4-methoxyphenylsulfonyl: Chromatography solvent: dichloromethane:tetrahydrofuran (7:1); TLC: R_f=0.18, dichloromethane:tetrahydrofuran (5:1); MS: m/z=566 (M+1).
Analysis for $C_{26}H_{26}F_3N_3O_6S \cdot 0.25\ H_2O$:
Calculated: C, 54.78; H, 4.69; N, 7.37
Found: C, 54.80; H, 4.69; N, 7.39

Example 16: R=anilinosulfonyl: Chromatography solvent: dichl romethane:acetonitrile (80:20); TLC: R_f=0.42, dichloromethane:ethyl acetate (70:30); MS: m/z=551(M+1).

Analysis for $C_{25}H_{25}F_3N_4O_5S \cdot 0.5\ H_2O$:
Calculated: C, 53.66; H, 4.68; N, 10.01
Found: C, 53.76; H, 4.68; N, 9.97

Example 17: R=butylaminosulfonyl: Purified by trituration with methyl tert-butyl ether; TLC: R_f=0.57, dichloromethane:ethyl acetate (70:30); MS: m/z=531(M+1).
Analysis for $C_{23}H_{29}F_3N_4O_5S$:
Calculated: C, 52.07; H, 5.51; N, 10.56
Found: C, 51.92; H, 5.52; N, 10.51

Example 18: R=methylaminosulfonyl: Purified by trituration with methyl tert-butyl ether; TLC: R_f=0.29, dichloromethane:ethyl acetate (70:30); MS: m/z=489(M+1).
Analysis for $C_{20}H_{23}F_3N_4O_5S$:
Calculated: C, 49.18; H, 4.74; N, 11.47
Found: C, 49.11; H, 4.75; N, 11.42

Example 19: R=cyclohexylaminosulfonyl: Purified by trituration with methyl tert-butyl ether; TLC: R_f=0.58, dichloromethane:ethyl acetate (70:30); MS: m/z=557(M+1).
Analysis for $C_{25}H_{31}F_3N_4O_5S$:
Calculated: C, 53.95; H, 5.61; N, 10.06
Found: C, 53.57; H, 5.59; N, 9.97

Example 20: R=4-nitrophenylsulfonyl: Chromatography solvent: dichloromethane:methanol (20:1); TLC: R_f=0.25, dichloromethane:-tetrahydrofuran:acetic acid (100:10:1); MS: m/z=581(M+1).
Analysis for $C_{25}H_{23}F_3N_4O_7S \cdot 0.25\ H_2O$:
Calculated: C, 51.33; H, 4.05; N, 9.58
Found: C, 51.20; H, 3.72; N, 9.41

Example 21: R=4-acetylaminophenylsulfonyl: Chromatography solvent: dichloromethane:methanol (20:1); TLC: R_f=0.12, dichloromethane:methanol (20:1); MS: m/z=593(M+1).

Analysis for $C_{27}H_{27}F_3N_4O_6S \cdot 1.0\ H_2O$:
Calculated: C, 53.11; H, 4.80; N, 9.18
Found: C, 53.31; H, 4.83; N, 8.94

Example 22: R=4-pyridylmethylsulfonyl: Chromatography solvent: dichloromethane:methanol (99:1 to 98:2); TLC: R_f=0.26, dichloromethane:methanol (95:5); MS: m/z=551(M+1).
Analysis for $C_{25}H_{25}F_3N_4O_5S \cdot 0.5\ H_2O$:
Calculated: C, 53.66; H, 4.68; N, 10.01
Found: C, 53.70; H, 4.60; N, 9.87

Example 23: R=3-pyridylmethylsulfonyl: Chromatography solvent: dichloromethane:methanol (99:1); TLC: R_f=0.28, dichloromethane:methanol (95:5); MS: m/z=551(M+1).
Analysis for $C_{25}H_{25}F_3N_4O_5S$:
Calculated: C, 53.66; H, 4.68; N, 10.01
Found: C, 53.75; H, 4.48; N, 9.98

Example 24: R=tert-butylaminosulfonyl: Chromatography solvent: dichloromethane:ethyl acetate (70:30); TLC: R_f=0.55, dichloromethane:ethyl acetate (70:30), MS: m/z= 531(M+1).
Analysis for $C_{23}H_{29}F_3N_4O_5S$:
Calculated: C, 52.07; H, 5.51; N, 10.56
Found: C, 52.19; H, 5.51; N, 10.52

Example 25: R=4-carboxyphenylsulfonyl: Reverse phase chromatography solvent: methanol:water (50:50); RP-TLC: R_f=0.36, methanol:water (65:35); MS: m/z=580(M+1).
Analysis for $C_{26}H_{24}F_3N_3O_7S$:
Calculated: C, 53.88; H, 4.17; N, 7.25
Found: C, 53.95; H, 4.19; N, 7.17

EXAMPLE 26

2-(2-Oxo-6-phenyl-3-sulfoamino-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide sodium salt.

Using a procedure similar to that described in Example 7 except that the sulfonyl chloride and triethylamine were replaced by a preformed complex of sulfur trioxide/triethylamine, the title compound was prepared. Purification was performed by ion-exchange chromatography on DOWEX 50, sodium form, with methanol:water (1:10) as the eluant. The appropriate fractions were combined, the methanol and triethylamine evaporated and the remaining solution lyophilized. The residual solid was partially dissolved in warm ethyl acetate, the solid was filtered and the solution evaporated to give a white solid; mp 140 °C (dec); RP-TLC: R_f=0.67, methanol:water (65:35); MS: m/z=474(M-1 for free acid), m/z=496(M-1 for sodium salt) by FAB.
Analysis for $C_{19}H_{19}F_3N_3O_6SNa \cdot 1.0\ H_2O$:
Calculated: C, 44.27; N, 4.10; N, 8.15
Found: C, 44.01; N, 4.15; N, 7.84

EXAMPLE 27

2-(3-Carboxymethylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

2-(3-Methoxycarbonylmethylsulfonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide was dissolved in methanol and treated with 1 N sodium hydroxide. The mixture was diluted with water, acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layers were washed (brine), dried and evaporated to give a solid, which was purified by reverse phase chromatography, with methanol:water (1:1) as the eluent. The resulting material was triturated with hexane to give the title compound; RP-TLC: R_f=0.58, methanol:water (65:35); 300 MHz NMR: 0.85 (2d,6), 2.15 (m,1), 4.30 (s,2), 4.50 (q,2), 4.65 (t,1), 6.25 (d,1), 7.45 (m,6), 7.75 (d,1), 9.20 (broad s, 1); MS: m/z=518(M+1).
Analysis for $C_{21}H_{22}F_3N_3O_7S$:
Calculated: C, 48.74; H, 4.28; N, 8.12
Found: C, 48.79; H, 4.52; N, 7.85

EXAMPLE 28

2-[3-(4-Aminophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

2-[3-(4-Nitrophenylsulfonyl)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide (167 mg) and 10% (w/w) palladium on carbon (42 mg) in a mixture of absolute ethanol (3 mL) and N,N-dimethylformamide (0.5 mL) was shaken under hydrogen (3.5 bar). After 24 hours and 28 hours, 32 mg and 42 mg respectively of 10% (w/w) palladium on carbon, were added. After 32 hours the reaction mixture was filtered through diatomatious earth and the solvent evaporated. The residue was dissolved in tetrahydrofuran, filtered through diatomaceous earth and the solvent evaporated. This residue was dissolved in dichloromethane and the product was precipitated by the addition of hexane to yield the title compound (105 mg) as a hemi-hydrate; mp 140-142 °C (dec); TLC: R_f=0.41; dichloromethane:methanol (95:5); MS: m/z=563(M-1) by FAB.
Analysis for $C_{26}H_{27}F_3N_4O_5S \cdot 0.5\ H_2O$:
Calculated: C, 54.44; H, 4.92; N, 9.77
Found: C, 54.65; H, 4.88; N, 9.79

EXAMPLE 29

2-[3-(4-Aminobenzylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

2-[3-(4-Nitrophenylsulfonyl)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide (0.20 g), 10% (w/w) palladium on carbon (0.05 g), and 2.5 mL absolute ethanol were combined and shaken under hydrogen (3.5 bar). After 4 hours the reaction mixture was filtered through diatomaceous earth and evaporated to yield 0.15 g of a light yellow solid. Chromatography, eluting with dichloromethane:methanol (40:1), followed by vernight vacuum drying, (50 °C, 27 Pa), yielded the title compound (0.08 g) as an off-white solid; mp 110-113 °C; TLC: R_f=0.19,

dichloromethane:methanol (20:1); MS: m/z=551(M+1).
Analysis for $C_{25}H_{25}F_3N_4O_5S \cdot 0.75\ H_2O$:
Calculated: C, 53.23; H, 4.74; N, 9.93
Found: C, 53.50; H, 4.68; N, 9.62

EXAMPLE 30

2-[3-(4-Trifluoroacetylaminophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide.

2-[3-(4-Aminophenylsulfonyl)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide was acylated using a procedure similar to that described in Example 1.a., except substituting trifluoroacetic anhydride for the sulfonyl chloride and dichloromethane for tetrahydrofuran, to give the title compound: Chromatography solvent: dichloromethane:methanol (30:1); TLC: R_f=0.33, dichloromethane:tetrahydrofuran:acetic acid (100:10:1); MS: m/z=647(M+1).
Analysis for $C_{27}H_{24}F_6N_4O_6S$:
Calculated: C, 50.16; H, 3.74; N, 8.67
Found: C, 50.42; H, 3.87; N,8.46

EXAMPLES 31-41

Using a procedure similar to that described in Example 7, except replacing triethylamine with pyridine, the following compounds of Formula I wherein R^0 is isopropyl, R^5 is hydrogen, R^6 is phenyl and R has the indicated value were prepared by sulfonylation of 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide using the corresponding sulfonyl chloride and purified by chromatography over silica gel, except as otherwise indicated.

Example 31: R=trifluoromethylsulfonyl: Chromatography solvent: dichloromethane:methanol (40:1); TLC: R_f=0.17,

dichloromethane:methanol (20:1); NMR: 8.75 (s,1), 7.45 (m,7), 6.22 (d,2), 4.63 (m,1), 4.50 (dd,2), 2.16 (m,1), 0.88 (dd,6); MS: m/z=528(M+1).

Analysis for $C_{20}H_{19}F_6N_3O_5S$:

Calculated: C, 45.54; H, 3.63; N, 7.97

Found: C, 45.64; H, 3.66; N, 7.78

Example 32: R=3-nitrophenylsulfonyl: Chromatography solvent: dichloromethane:methanol (30:1); TLC: R_f=0.5, dichloromethane:methanol:acetic acid (99:10:1); NMR: 10.20 (s,1), 8.65 (m,2), 8.47 (d,1), 8.30 (d,1), 7.85 (dd,1), 7.47 (m,5), 7.30 (d,1), 6.18 (d,1), 4.58 (dd,1), 4.35 (dd,2), 2.14 (m,1), 0.82 (dd,6); MS: m/z=581(M+1).

Analysis for $C_{25}H_{23}N_4O_7F_3S$:

Calculated: C, 51.72; H, 3.99; N, 9.65

Found: C, 51.80; H, 4.08; N, 9.57

Example 33: R=isopropylaminosulfonyl: Chromatography solvent: dichloromethane:tetrahydrofuran (85:15), followed by trituration with diethyl ether; TLC: R_f=0.44, dichloromethane:-methanol (20:1); NMR: 8.73 (d,1), 8.32 (s,1), 7.58 (m ,1), 7.43 (m,6), 6.72 (d,1), 4.63 (dd,1), 4.50 (dd,2), 3.40 (m,1), 2.15 (m,1), 1.05 (m,1), 0.89 (d,3), 0.83 (d,3); MS: m/z=517(M+1).

Analysis for $C_{22}H_{27}F_3N_4O_5S$:

Calculated: C, 51.16; H, 5.27; N, 10.85

Found: C, 50.90; H, 5.24; N, 10.77

Example 34: R=4-(N,N-dimethylcarbamoylmethyl)phenylsulfonyl: Purified by trituration with diethyl ether; TLC: R_f=0.21, dichloromethane:methanol (20:1); NMR (DMSO/D_2O): 7.88 (d,2), 7.42 (m,8), 6.16 (d,1), 4.42 (dd,2), 4.05 (d,1), 3.80 (s,2), 3.03 (s,3), 2.84 (s,3), 2.15 (m,1), 0.85 (dd,6); MS: m/z=621(M+1).

Analysis f r $C_{29}H_{31}F_3N_4O_6S \cdot 0.50\ H_2O$:

Calculated: C, 55.32; H, 5.12; N, 8.90

Found: C, 55.33; H, 5.13; N, 8.83

Example 35: R=benzoylaminosulfonyl: Purified by trituration with methyl tert-butyl ether; TLC: R_f=0.36, dichloromethane:methanol (9:1); NMR (DMSO/D_2O): 6.25 (d,1, J=7.7), 4.55 (d,1, J=16.5), 4.40 (d,1, J=16.5), 4.02 (d,1, J=2.9), 2.22 (m,1), 0.84 (d,3, J=6.8), 0.76 (d,3, J=6.8); MS: FAB m/z=579(M+1), 577(M-1).

Analysis for $C_{26}H_{25}F_3N_4O_6S$:

Calculated: C, 53.98; H, 4.36; N, 9.68

Found: C, 53.65; H, 4.44; N, 9.67

Example 36: R=methoxycarbonylaminosulfonyl: Purified by sequential trituration, first with diethyl ether:hexanes (1:1) then with methyl tert-butyl ether; TLC: R_f=0.20, dichloromethane:methanol (9:1); NMR (DMSO/D_2O): 7.44 (m,6), 6.25 (d,1, J=7.5), 4.56 (d,1, J=16.4), 4.42 (d,1, J=16.4), 4.04 (d,1, J=2.6), 3.65 (s,3), 2.23 (m,1), 0.85 (d,3, J=6.6), 0.78 (d,3, J=6.7); MS: FAB m/z=533(M+1), 531(M-1).

Analysis for $C_{21}H_{23}F_3N_4O_7S \cdot 0.5\ H_2O$:

Calculated: C, 46.58; H, 4.47; N, 10.35

Found: C, 46.77; H, 4.39; N, 10.29

Example 37: R=2,2,2-trifluoroethylsulfonyl: Purified by trituration with methyl tert-butyl ether:hexanes; TLC: R_f=0.83, dichloromethane:tetrahydrofuran:acetic acid (100:10:1); NMR (DMSO/D_2O): 7.45 (m,6), 6.28 (d,1, J=7.6), 4.52 (m,4), 4.05 (d,1, J=2.6), 2.23 (m,1), 0.86 (d,3, J=6.8), 0.79 (d,3, J=6.8); MS: m/z=542(M+1).

Analysis for $C_{21}H_{21}F_6N_3O_5S \cdot 0.5\ H_2O$:

Calculated: C, 45.82; H, 4.03; N, 7.63

Found: C, 46.11; H, 4.02; N, 7.60

Example 38: R=2,2,2-trifluoroethylaminosulfonyl: Purified by trituration with diethyl ether:ethyl acetate (20:1); TLC: R_f=0.75, dichloromethane:tetrahydrofuran (9:1); NMR (DMSO/D_2O): 7.44 (m,6), 6.23 (d,1, J=7.6), 4.56 (d,1, J=16.5), 4.31 (d,1, J=16.5), 4.06 (d,1, J=2.9), 3.71 (q,2, J=9.6), 2.24 (m,1), 0.86 (d,3, J=6.8), 0.79 (d,3, J=6.8); MS: m/z=557(M+1).

Analysis for $C_{21}H_{22}F_6N_4O_5S \cdot 0.5\ H_2O$:
Calculated: C, 44.60; H, 4.10; N, 9.91
Found: C, 44.56, H, 3.92; N, 9.98

Example 39: R=acetylaminosulfonyl: Reverse phase chromatography solvent: methanol:water (50:50); TLC: R_f=0.27, dichloromethane:methanol (90:10); NMR: 7.70 (d,1, J=7.6), 7.43 (m,5), 6.24 (d,1, J=7.6), 4.56 (d,1, J=16.4), 4.41 (d,1, J=16.4), 4.04 (d,1), 2.22 (m,1). 1.96 (s,3), 0.85 (d,3, J=6.8), 0.78 (d,3, J=6.8); MS: FAB m/z=517(M+1), 515(M-1).
Analysis for $C_{21}H_{23}F_3N_4O_6S \cdot 1.0\ H_2O$:
Calculated: C, 47.19; H, 4.71; N, 10.48
Found: C, 47.13; H, 4.62; N, 10.52

Example 40: R=ethoxycarbonylaminosulfonyl: Purified by trituration using hexane:diethyl ether (5:1); TLC: R_f=0.16, dichloromethane:methanol (10:1); NMR (DMSO/D20): 7.44 (m,6), 6.26 (d,1), 4.48 (dd,2), 4.12 (q,2), 4.05 (d,1), 2.25 (m,1), 1.80 (t,3), 0.85 (d,3), 0.78 (d,3); MS: m/z=FAB 547(M+1), 545(M-1).
Analysis for $C_{22}H_{25}F_3N_4O_7S$:
Calculated: C, 48.35; H, 4.61; N, 10.25
Found: C, 48.16, H, 4.69; N, 10.06

Example 41: R=cyanomethylsulfonyl: Chromatography solvent: dichloromethane:methanol (9:1), followed by trituration with diethylether; TLC: R_f=0.5, dichloromethane:methanol (9:1); NMR (DMSO/D_2O): 7.47 (m,6), 6.24 (d,1, J=7.5), 4.57 (d,1, J=16.3), 4.42 (d,1, J=16.3), 4.06 (d,1, J=2.9), 2.22 (m,1), 0.86 (d,3, J=6.8), 0.78 (d,3, J=6.8); MS: m/z=499(M+1).
Analysis for $C_{21}H_{21}F_3N_4O_5S \cdot 0.25\ H_2O$:
Calculated: C, 50.15; H, 4.31; N, 11.14
Found: C, 50.14; H, 4.10; N, 11.01

EXAMPLE 42

2-[3-(3-Aminophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

Using a procedure similar to that described in Example 29, 2-[3-(3-nitrophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide was converted into the title compound. Chromatography solvent: dichloromethane:methanol (40:1); TLC: R_f=0.20, dichloromethane:-methanol (20:1); NMR: 9.43 (s,1), 8.62 (d,1), 7.48 (m,6), 7.18 (dd,1), 7.09 (dd,1), 7.03 (d,1), 6.77 (dd,1), 6.15 (d,1), 5.62 (broad s,2), 4.63 (m,1), 4.45 (dd,2), 2.15 (m,1), 0.87 (dd,6); MS: m/z=551(M+1).

Analysis for $C_{25}H_{25}N_4O_5F_3S$:

Calculated: C, 54.54; H, 4.58; N, 10.18

Found: C, 54.56; H, 4.74; N, 10.06

EXAMPLE 43

2-[3-(3-Acetylaminophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide.

Using a procedure similar to that described in Example 7.1., except replacing trifluoroacetic anhydride with acetic anydride, 2-[3-(3-aminophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide was converted into the title compound. Chromatography solvent: dichloromethane:methanol (35:1); TLC: R_f=0.24, dichloromethane:-methanol (20:1); NMR (DMSO/D_2O): 8.22 (s,1) 7.73 (d,1), 7.60 (d,1), 7.5 (br m, 7), 6.16 (d,1), 4.40 (m,2), 4.02 (d,1), 2.12 (m,1), 2.09 (s,3), 0.80 (d,2); MS: m/z=593(M+1).

Analysis for $C_{27}H_{27}F_3N_4O_6S \cdot 0.50\ H_2O$:

Calculated: C, 53.91; H, 4.69; N, 9.31

Found: C, 54.07; H, 4.86; N, 9.10

EXAMPLE 44

2-[3-[4-(N-Methylsulfonylcarbamoyl)phenylsulfonylamino]-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

A solution of 2-[3-(4-carboxyphenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide (0.600 g), methanesulfonamide (0.1983 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.2327 g), and 4-dimethylaminopyridine (0.1472 g) in dichloromethane (4.5 mL) was stirred. After 4 hours and 7 hours, 0.0167 g and 0.0172 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added respectively and stirring was continued for 24 hours. Methanesulfonamide (0.0180 g) was added, the solution was stirred for 25 hours. The reaction was diluted with ethyl acetate (100 mL), and was washed (0.1 N hydrochloric acid (twice), water, brine), dried (sodium sulfate) and evaporated to give an orange brown solid. Reverse phase chromatography, eluting with methanol:water (40:60), followed by evaporation of the methanol and additon of 1N hydrochloric acid precipitated the title compound as a white powder (0.196 g). RP-TLC R_f=0.66, methanol:water 65:35 pH 6.7; NMR (DMSO/D2O): 8.06 (s,4), 7.64 (d,1), 7.41 (m,6), 6.16 (d,1), 4.48 (d,1), 4.32 (d,1), 4.03 (d,1), 3.37 (s,3), 2.21 (m,1), 0.82 (d,3), 0.75 (d,3); MS: m/z=657(M+1).

Analysis for $C_{27}H_{27}F_3N_4O_8S_2 \cdot 1.0\ H_2O$:

Calculated: C, 48.07; H, 4.33; N, 8.30

Found: C, 47.80; H, 4.29; N, 8.20

EXAMPLES 45-46

Using a procedure similar to that described in Example 44, except replacing methanesulfonamide with the required sulfonamide, the foll wing compounds of Formula I wherein R^0 is isopropyl, R^5 is hydr gen, R^6 is phenyl and R has the indicated value were prepared.

Example 45: R=4-[N-(4-chlorophenylsulfonyl)carbamoyl]-phenylsulfonyl: Chromatography solvent: dichloromethane:methanol (50:1); TLC: R_f=0.31, dichloromethane:methanol:acetic acid (100:5:1); NMR: 9.87 (s,1), 8.70 (d,1), 8.01 (d,2), 7.91 (m,4), 7.57 (d,2), 7.38 (m,6), 6.13 (d,1), 4.60 (m,1), 4.38 (dd,2), 2.12 (m,1), 0.85 (dd,6); MS: FAB m/z=751(M-1), 753(M+1).
Analysis for $C_{32}H_{28}ClF_3N_4O_8S_2 \cdot 1.0\ H_2O$:
Calculated: C, 49.84; H, 3.92; N, 7.27
Found: C, 49.63; H, 3.77; N, 7.09

Example 46: R=4-[N-(2-methylphenylsulfonyl)carbamoyl]-phenylsulfonyl: Reverse phase chromatography solvent: methanol:water (40:60); RP-TLC: R_f=0.48, methanol:water (65:35 at pH 6.7); NMR: 10.01 (s,1), 8.68 (d,1), 8.02 (m,1), 7.35 (m,1), 6.12 (d,1), 4.59 (dd,1), 4.44 (d,1), 4.33 (d,1), 2.61 (s,3), 2.11 (m,1), 0.85 (d,3). 0.79 (d,3); MS: m/z=733(M+1).
Analysis for $C_{33}H_{31}F_3N_4O_8S_2 \cdot 0.5H_2O$:
Calculated: C, 53.45; H, 4.35; N, 7.55
Found: C, 53.37; H, 4.44; N, 7.73

EXAMPLE 47

2-[3-(4-Methylsulfonylaminophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide.

Using a procedure similar to that described in Example 30, except using methanesulfonyl chloride in place of trifluoroacetic anhydride, the title compound was prepared. Chromatography solvent: dichloromethane:tetrahydrofuran (20:1); TLC: R_f=0.23, dichloromethane:tetrahydrofuran:acetic acid (99:10:1); NMR: 10.45 (s,1), 9.60 (s,1), 8.70 (d,1), 7.90 (d,2), 7.37 (d,2), 6.14 (d,1), 4.60 (dd,1), 4.41 (dd,2), 3.15 (s,3), 2.15 (m,1), 0.88 (dd,6); MS: m/z=629(M+1).

Analysis for $C_{26}H_{27}F_3N_4O_7S_2 \cdot 0.05\ C_{15}H_{24}O$:
Calculated: C, 50.22; H, 4.44; N, 8.76
Found: C, 50.20; H, 4.49; N, 8.69

EXAMPLE 48

2-[3-(4-Methoxycarbonylaminophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopyropyl-2-oxopropyl)-acetamide.

Using a procedure similar to that described in Example 30, except using methyl chloroformate in place of trifluoroacetic anhydride, and purification by trituration using hexane:diethyl ether (2:1), the title compound was obtained; TLC: R_f=0.26, chloroform:tetrahydrofuran:acetic acid (99:10:1); NMR (DMSO/D_2O): 10.12 (s,1), 7.85 (d,2), 7.62 (d,2), 7.40 (m,6), 6.15 (d,1), 4.40 (q,2), 4.03 (d,1), 2.22 (m,1), 0.83 (d,3), 0.76 (d,3);
MS: m/z=609(M+1).
Analysis for $C_{27}H_{27}F_3N_4O_7S \cdot 0.5\ H_2O$:
Calculated: C, 52.51; H, 4.56; N, 9.22
Found: C, 52.63; H, 4.57; N, 8.87

EXAMPLES 49-50

Using a procedure similar to that described in Example 7, except using pyridine in place of triethylamine, the following compounds of Formula I wherein R^0 is isopropyl, R^5 and R^6 are each hydrogen and R has the indicated value were prepared by sulfonylation of 2-(3-amino-2-oxo-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide (Example 75 in European Patent Application, Publication Number 509769) with the corresponding sulfonyl chloride. Except as otherwise noted, the product was purified by chromatography over silica gel.

Example 49: R=4-acetylaminophenylsulfonyl: Chromatography solvent: dichloromethane:methanol (gradient 98:2 to 95:5); TLC: R_f=0.46, dichloromethane:methanol (90:10); NMR: 10.31 (s,1), 9.35

(s,1), 8.87 (d,1, J=6.7), 7.78 (d,2), 7.70 (d,2), 7.29 (m,2), 6.17 (t,1, J=7.1), 4.63 (m,3), 2.18 (m,1), 2.06 (s,3), 0.94 (d,3, J=6.8), 0.91 (d,3, J=6.8); MS: m/z=417(M+1).

Analysis for $C_{21}H_{23}F_3N_4O_6S$:

Calculated: C, 48.84; H, 4.49; N, 10.85

Found: C, 48.80; H, 4.56; N, 10.50

Example 50: R=benzylsulfonyl: Purified by recrystallization from ethyl acetate; TLC: R_f=0.41, dichloromethane:methanol (95:5); NMR: 8.95 (d,1, J=6.5), 8.74 (s,1), 7.40 (dd,1), 7.33 (s,5), 7.18 (dd,1, J=1.7, 7.3), 6.17 (t,1, J=7.1), 4.55 (s,2), 2.21 (m,1), 0.97 (d,3, J=6.8), 0.95 (d,3, J=6.8); MS: m/z=474(M+1).

Anaylsis for: $C_{20}H_{22}F_3N_4O_5S$:

Calculated: C, 50.74; H, 4.68; N, 8.88

Found: C, 50.76; H, 4.67; N, 8.86

EXAMPLE 51

2-(3-Ethylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

To a solution of 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide (0.305 g) and 2,6-lutidine (0.1 mL) in dimethylformamide (4.5 mL) was added ethyl iodide (0.09 mL). After 20 hours, further charges of 2,6-lutidine (0.1 mL) and ethyl iodide (0.09 mL) were made. After 5 hours, the reaction mixture was added to ethyl acetate and water and the organic phase was separated, washed (brine), dried ($MgSO_4$), and evaporated. Chromatography (twice), eluting with dichloromethane:methanol (gradient, 99.5:0.5, 99:1) gave the title compound (68 mg) as a yellow solid; TLC: R_f=0.42, dichloromethane:methanol (98:2); MS: m/z=424(M+1).

Analysis for $C_{21}H_{24}F_3N_3O_3$:

Calculated: C, 59.56; H, 5.71; N, 9.92

Found: C, 59.17; H, 5.76; N, 9.52

EXAMPLE 52

2-(2-Oxo-3-phenethylamino-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

Using a procedure similar to that described for Example 51, but using 2-phenethyl bromide and sodium iodide in place of ethyl iodide, omitting the second addition of reagents and purifying by chromatography, eluting with dichloromethane:methanol (gradient, 99.5:1, 97:3), the title product was obtained as a light yellow foam; TLC: R_f=0.41, dichloromethane:methanol (98:2); MS: m/z=500(M+1).
Analysis for $C_{27}H_{28}F_3N_3O_3 \cdot 0.4\ H_2O$:
Calculated: C, 63.99; H, 5.72; N, 8.29
Found: C, 63.93; H, 5.62; N, 8.29

EXAMPLE 53

2-(3-Methylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

Using a procedure similar to that described under Example 49.j. of European Patent Application, Publication Number 509769, for the basic hydrolysis of the analogous 3-(N-trifluoroacetylamino)-compound to the 3-amino-compound, but using the following extractive work-up, the title compound was prepared from 2-[3-(N-trifluoroacetyl-N-methylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide. On completion of hydrolysis, ethyl acetate and brine were added. The organic phase was separated, washed (brine), dried ($MgSO_4$), and evaporated. The resultant solid was triturated with diethyl ether, chromatographed, eluting with dichloromethane:methanol (96:4), and dried overnight under vacuum to give the title product as a white solid; TLC: R_f=0.20, dichl romethane:methanol (96:4); MS: m/z=410(M+1).
Analysis for $C_{20}H_{22}F_3N_3O_3 \cdot 0.5\ H_2O$:
Calculated: C, 57.41; H, 5.54; N, 10.04
Found: C, 57.42; H, 5.34; N, 9.78

The starting material was prepared as follows.

a. 2-[3-(N-Trifluoroacetyl-N-methylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide.

To a solution of 2-(3-trifluoroacetylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide (Example 167 in European Patent Application, Publication Number 509769) (200 mg) in dimethylformamide (2 mL) was added sodium carbonate (128 mg) and methyl iodide (130 µL). The mixture was stirred in a stoppered vessel overnight. Ethyl acetate and brine were added. The organic phase was separated, washed (brine), dried ($HgSO_4$), and evaporated. Chromatography, eluting with dichloromethane:methanol (98:2), gave the title product (80 mg) as a white solid; TLC: R_f=0.15, dichloromethane:methanol (98:2); MS: m/z=506(M+1).

EXAMPLE 54

2-[3-(4-Fluorobenzylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

2-[3-[N-(4-Fluorobenzyl)-N-trifluoroacetylamino]-2-oxo-6-pheny-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide was subjected to a procedure similar to that described in Example 53, but purifying by chromatography, eluting with dichloromethane:methanol (gradient, 99.5:0.5, 99:1), to give the title compound; TLC: R_f=0.45, dichloromethane:methanol (98:2); MS: m/z=504(M+1).

Analysis for $C_{26}H_{25}F_4N_3O_3 \cdot 0.3\ H_2O$:

Calculated: C,61.36; H, 5.07; N, 8.25

Found: C,61.45; H, 5.00; N, 8.23

The starting material was prepared as follows.

a. 2-[3-[N-Trifluoroacetyl-N-(4-fluorobenzyl)amino]-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide

Using a procedure similar to that described for Example 53.a. except using 4-fluorobenzyl bromide and sodium iodide in place of methyl iodide and purifying by chromatography, eluting with dichloromethane:methanol (gradient, 99.5:0.5, 98:2), the title product was prepared as a colorless gum; TLC: R_f=0.29, dichloromethane:acetone (95:5); MS: m/z=600(M+1).

EXAMPLE 55

2-[3-[N-Trifluoroacetyl-N-(4-methoxybenzyl)amino]-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide was subjected to a procedure similar to that described in Example 53, but purifying by chromatography, eluting with dichloromethane:methanol (gradient, 99:1, 98:2), to give the title compound as a white solid; TLC: R_f=0.24, dichloromethane:methanol (98:2); MS: m/z=516(M+1).

Analysis for $C_{27}H_{28}F_3N_3O_4 \cdot 0.5\ H_2O$:

Calculated: C, 61.83; H, 5.57; N, 8.01

Found: C, 61.58; H, 5.57; N, 7.77

The starting material was prepared as follows.

a. 2-[3-[N-(4-Methoxybenzyl)-N-trifluoroacetylamino]-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide.

Using a procedure similar to that described for Example 53.a., except using 4-methoxybenzyl bromide and sodium iodide in place of methyl iodide and purifying by chromatography, eluting with dichloromethane:methanol (99:1), the title compound was prepared; TLC: R_f=0.33, dichloromethane:methanol (98:2); MS: m/z=612(M+1).

EXAMPLE 56

2-(3-Benzylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

2-[3-(N-Benzyl-N-trifluoroacetylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)-acetamide was subjected to a procedure similar to that described for Example 53, but purifying by chromatography, eluting with dichloromethane:methanol (gradient, 99.5:0.5, 98:2), to give the title compound as a white solid; TLC: R_f=0.45, dichloromethane:methanol (98:2); MS: m/z=486(M+1).
Analysis for $C_{26}H_{26}F_3N_3O_3 \cdot 0.2\ H_2O$:
Calculated: C, 63.84; H, 5.44; N, 8.59
Found: C, 63.86; H, 5.68; N, 8.31

The starting material was prepared as follows.

a. 2-[3-(N-Trifluoroacetyl-N-benzylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide.

Using a procedure similar to that described for Example 53.a. except employing benzyl bromide and sodium iodide in place of methyl iodide, heating the reaction mixture at 50 °C, and purifying by chromatography, eluting with dichloromethane:methanol (99:1), the title product was prepared; R_f=0.35, dichloromethane:methanol (98:2); MS: m/z=582(M+1).

EXAMPLE 57

2-[3-(2,2,2-Trifluoroethoxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropylpropyl)acetamide.

To a solution f 2-(3-amin -2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-(3,3,3-trifluoro-1-isopropyl-2-oxopropyl)acetamide (400 mg) in dichloromethane (8 mL) at 0 °C was added pyridine (320 mg)

followed by 2,2,2-trifluoroethyl chloroformate (180 uL). After 1 hour the reaction mixture was diluted with diethyl ether and quenched with ice. The phases were separated; and the organic phase was washed (dilute hydrochloric acid, brine), dried and evaporated to afford a gummy solid. This solid was triturated with diethyl ether:hexanes (10 mL, 1:1) to afford a white powder which was collected by filtration and dried under vacuum to yield the title compound (388 mg); mp 196-198 °C; TLC: R_f=0.68, chloroform:methanol (20:1); NMR (DMSO/D_2O): 7.91 (d,1, J=8.19), 7.30-7.50 (m,5), 6.29 (d,1, J=8.19), 4.83 (d,1, J=9), 4.75 (d,1, J=9), 4.71 (d,1, J=16), 4.47 (d,1, J=16.4), 2.23 (m,1), 0.86 (d,3, J=6.7), 0.80 (d,3, J=6.7); MS: m/z=522(M+1).

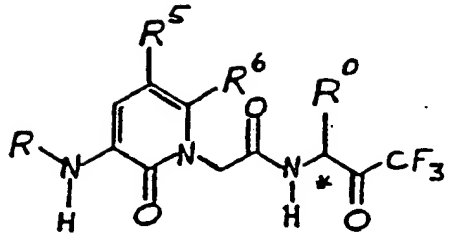
Analysis for $C_{22}H_{21}F_6N_3O_5 \cdot 0.5\ H_2O$:

Calculated: C, 49.82; H, 4.18; N, 7.92

Found: C, 49.96; H, 4.21; N, 7.80

The intermediate 2,2,2-trifluoroethyl chloroformate was prepared using a procedure similar to that described in U.S. Patent Number 3,852,464, except that bis(trichloromethyl) carbonate was used in place of phosgene.

FORMULAE



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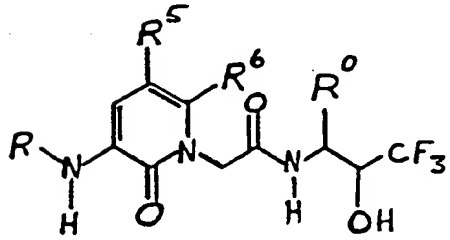

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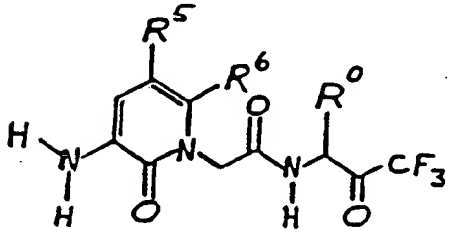

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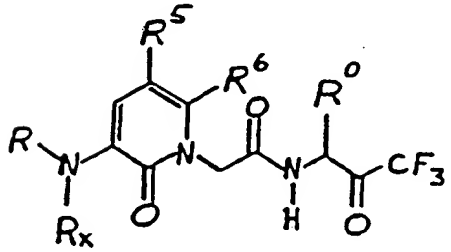
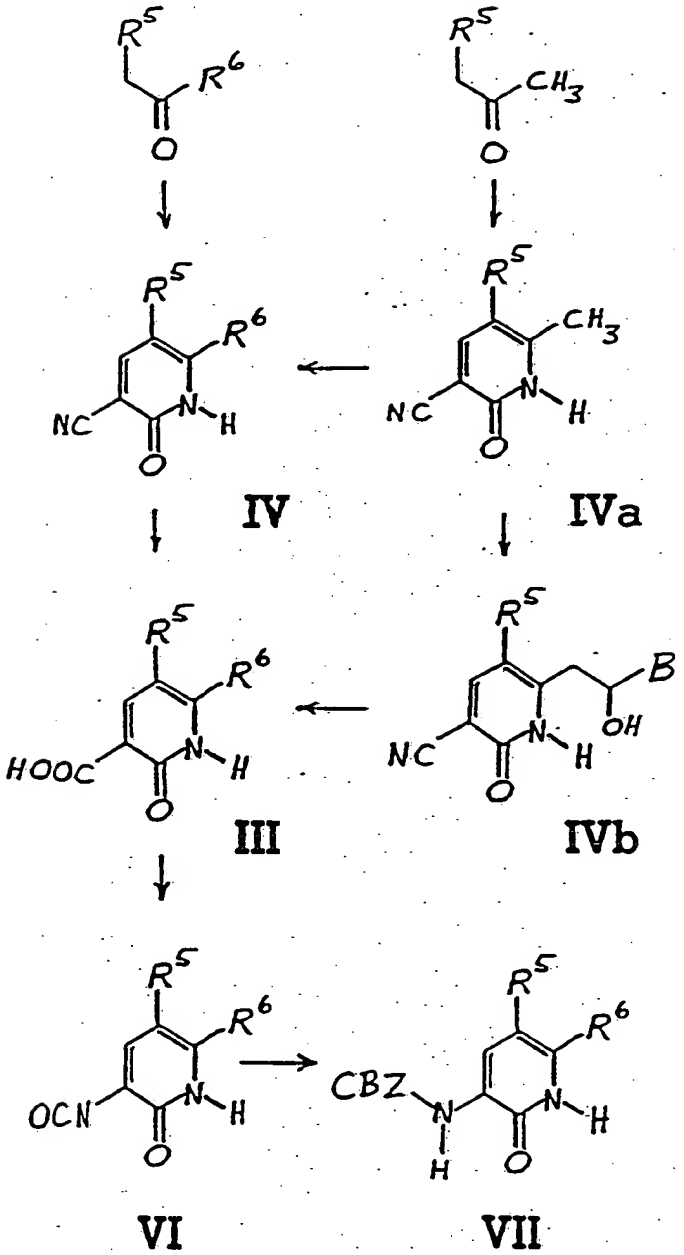


Vb

SCHEME I



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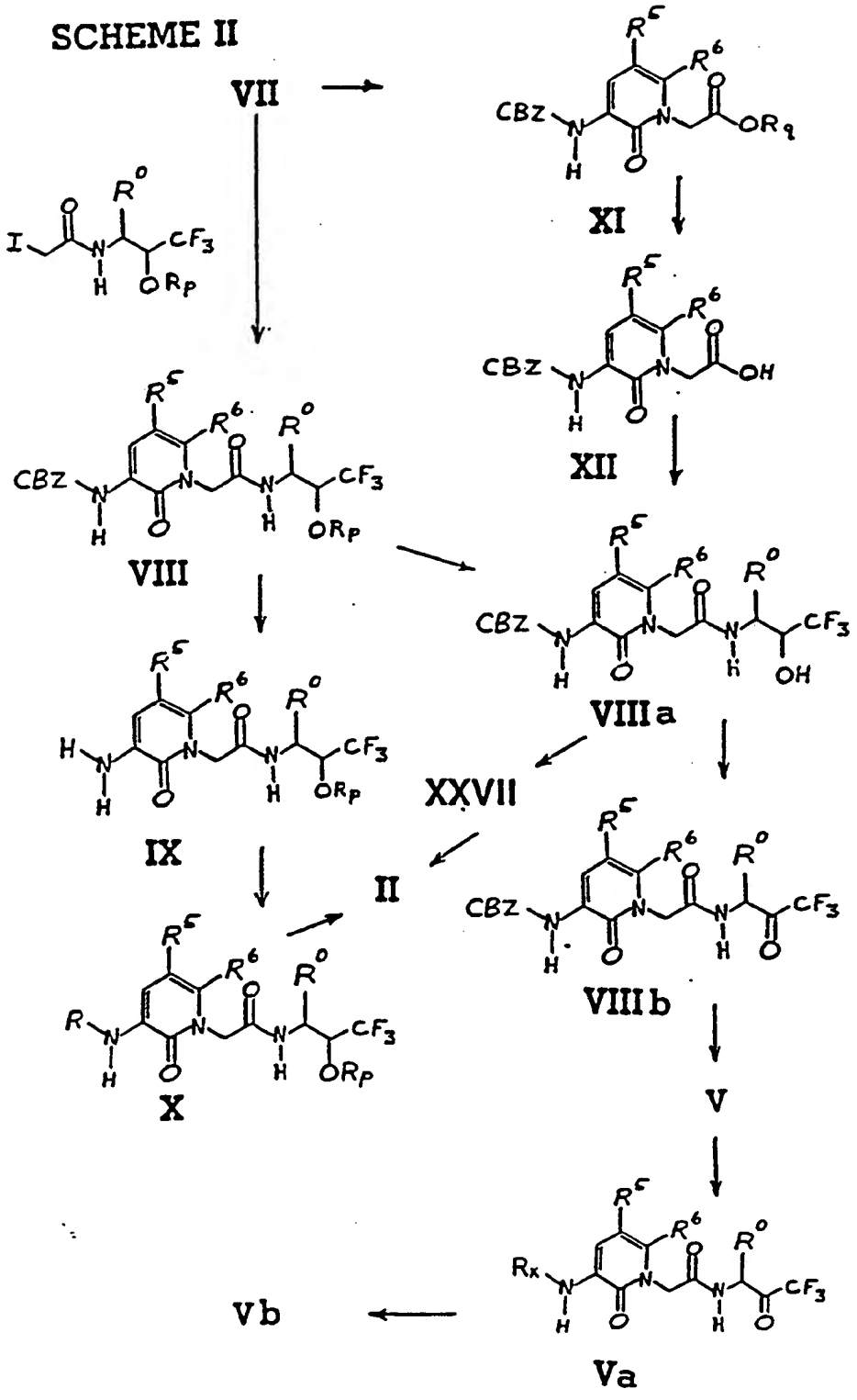
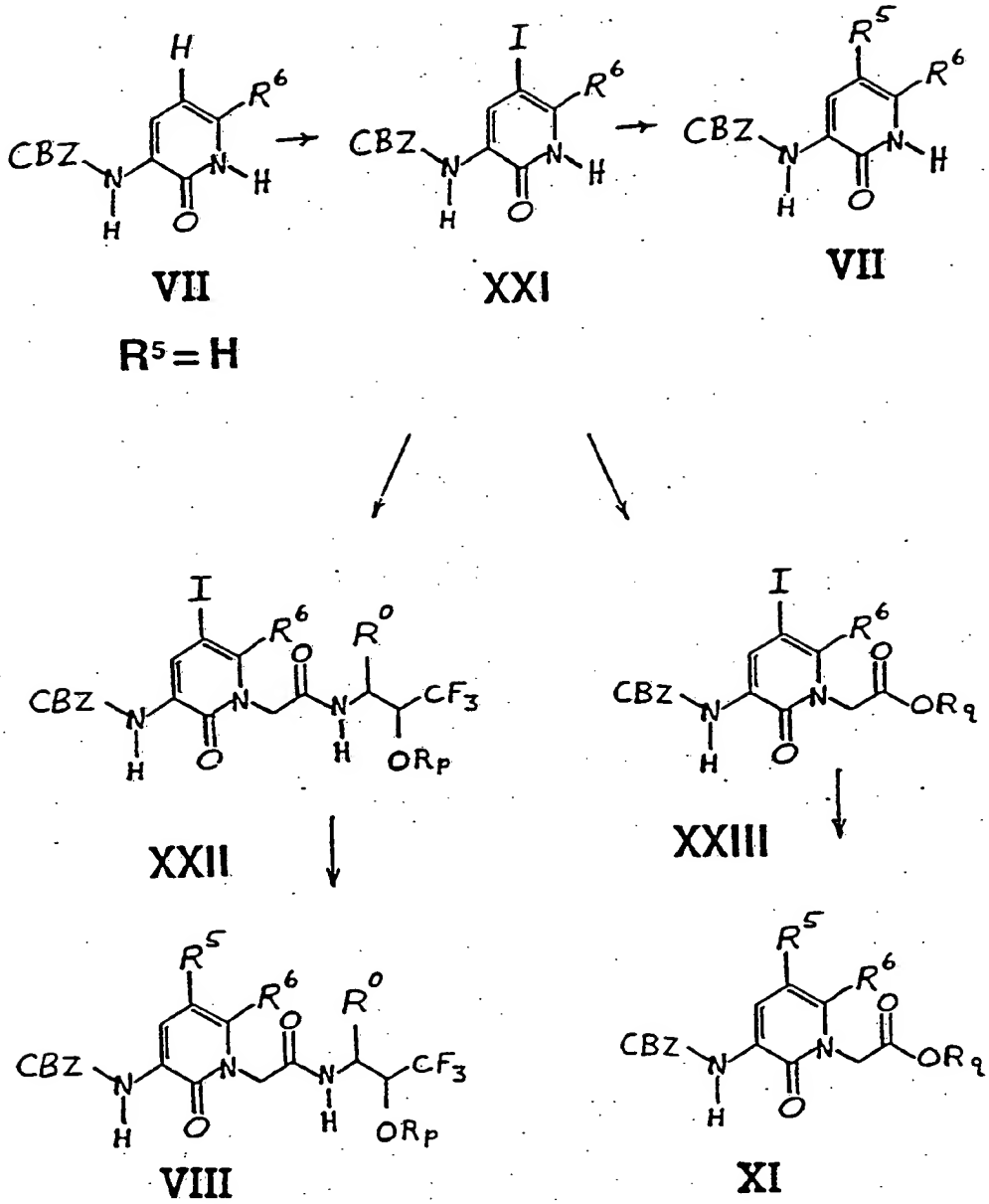
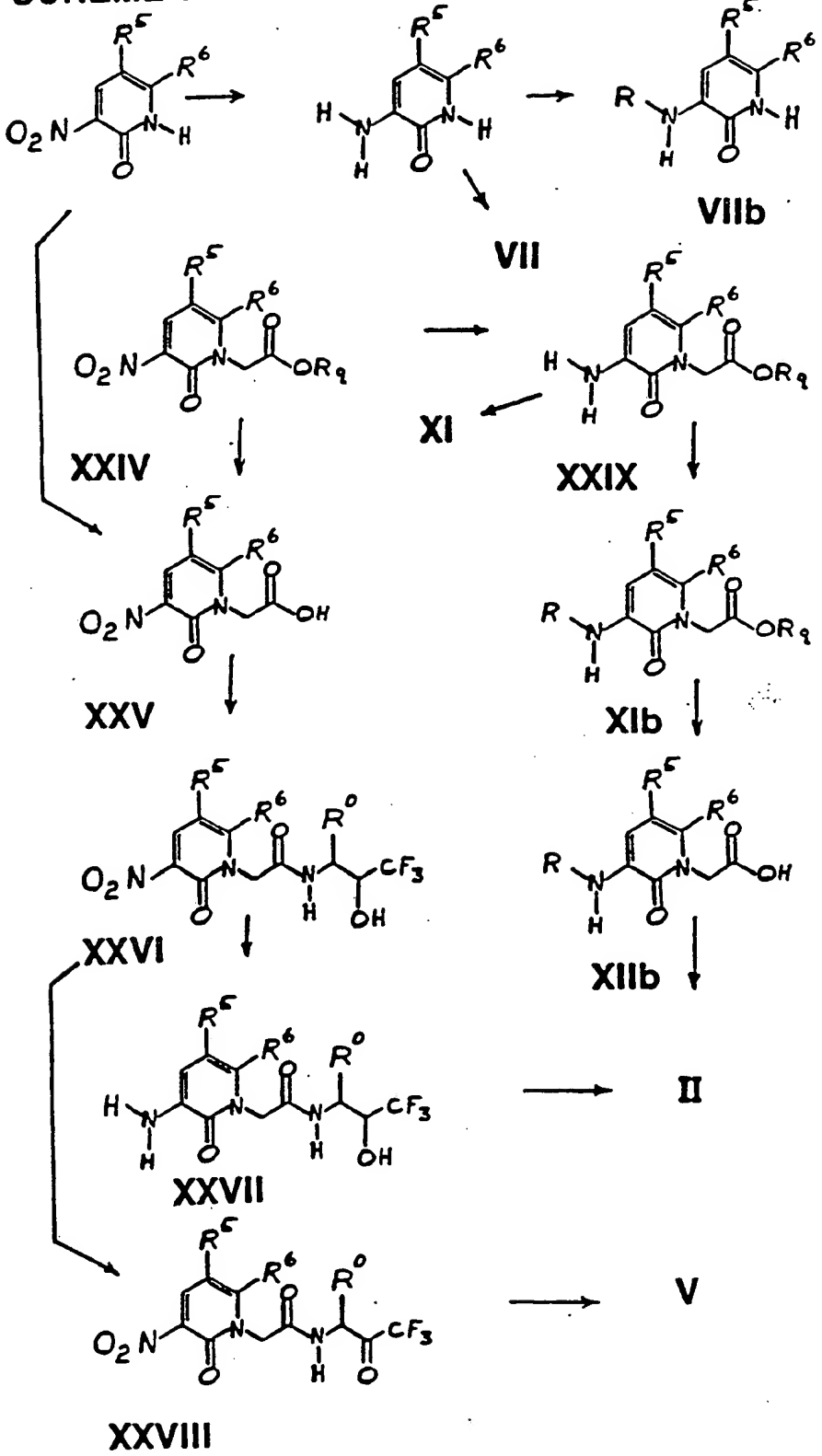


SCHEME III



SCHEME IV



What is claimed is:

1. A compound of formula I (formula set out hereinbelow) wherein:

R^0 is (1-5C)alkyl;

R is 2,2,2-trifluoroethoxycarbonyl or 2,2,2-trifluoroethylaminocarbonyl; or

R is a sulfonyl group of formula D.W.SO_2- in which D.W-, taken together, is hydroxy, amino, di(lower alkyl)amino, 2,2,2-trifluoroethylamino, 3,3,3-trifluoropropyl, 2,2,2-trifluoroethyl or trifluoromethyl; or

V is a direct bond, imino, carbonylimino, oxycarbonylimino or iminocarbonylimino; and

D is as defined below; or

R is a group G as defined below;

The group D or G is (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-3C)alkyl, aryl, aryl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)-alkyl wherein an alkyl carbon of G not bonded to the pyridone 3-amino nitrogen may bear an oxo group and wherein an aryl or heteroaryl moiety may bear one or more halogeno, nitro, methyl or trifluoromethyl groups and further wherein the group D or G may bear one or more substituents selected from a group consisting of hydroxy, lower alkoxy, lower acyloxy, COORa, CH_2COORa, CONRbRc, CH_2CONRbRc, $COO(CH_2)_2NReRf$, cyano, SO_2R^1, $CONRdSO_2R^1$, NReRf, NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCONRiRj, $NRkSO_2R^3$, SO_2NRlRm, $SO_2NRnCOR^4$ and $P(O)(ORa)_2$ in which

Q is oxygen or sulfur;

Ra-Rn are independently hydrogen, benzyl or lower alkyl; or, independently, a group NRbRc, NReRf, NRiRj or NRlRm is a cyclic radical selected from a group consisting of 1-pyrrolidinyl, piperidino, morpholino or 1-piperazinyl which may bear a lower alkyl substituent at the 4-position; or, independently, a group NReRf is a cyclic radical selected from a group consisting of 2-pyrrolidinon-1-yl, succinimido, oxazolidin-2-on-3-yl, 2-benzoxazolinon-3-yl, phthalimido and cis-hexahydrophthalimido; and

R^1-R^4 are independently trifluoromethyl, (1-6C)alkyl,

(3-6C)cycloalkyl, aryl or heteroaryl in which the aryl or heteroaryl may bear one or more substituents selected from a group consisting of lower alkyl, hydroxy, lower alkoxy, halogeno or trifluoromethyl;

Each of R^5 and R^6 is, independently, hydrogen or lower alkyl; or

One of R^5 and R^6 is hydrogen or methyl and the other of R^5 and R^6 is a radical of formula B.Y- in which

B is aryl or heteroaryl, which aryl or heteroaryl independently may bear one or more of the substituents defined for D or G or an aryl or heteroaryl moiety thereof;

Y is a direct bond, methylene, ethylene or trans-vinylene; and

provided that no aliphatic carbon is bonded to more than one nitrogen or oxygen, except as part of a cyclic ketal or where the nitrogen bears a carbonyl group; or,

for a compound of formula I which is acidic or basic, a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein

R^0 is ethyl or isopropyl;

D.W-, taken together, is amino, 2,2,2-trifluoroethylamino or 2,2,2-trifluoroethyl;

W is a direct bond or imino;

G is (1-3C)alkyl, aryl(1-C)alkyl or heteroaryl(1-2C)alkyl which may bear one or more substituents as defined in Claim 1 for G or a part thereof;

(1-6C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, 3-methylbutyl, 1-ethylpropyl, hexyl or 4-methylpentyl; (3-6C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl; the (1-3C)alkyl portion of (3-6C)cycloalkyl-(1-3C)alkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl is methylene, ethylene or trimethylene; aryl is phenyl, indenyl or naphthyl; heteroaryl is furyl, imidazolyl, tetrazolyl, pyridyl (or its N-oxide), thienyl, pyrimidinyl (r its N- xide), indolyl or quinolinyl (or its N-oxide); lower alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; lower acyloxy is acetoxy; lower alkoxy is methoxy, ethoxy,

propoxy, isoproxy or t-butoxy; halogeno is bromo, chloro or fluoro; COORa is carboxy or methoxycarbonyl; NRgCHO is formylamino; $NRgCOR^2$ is acetylamino or trifluoroacetylamino; and $CONRdSO_2R^1$ is N-phenylsulfonylcarbamoyl or N-(4-chlorophenylsulfonyl)carbamoyl.

3. A compound as claimed in Claim 1 or 2 wherein R^0 is isopropyl; D is methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, phenyl, benzyl, phenethyl, pyridyl, thienyl, 5-tetrazolyl, thiazolyl, quinolinyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, 2-(pyridyl)ethyl, 2-(thienyl)ethyl or 2-(thiazolyl)ethyl wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group D may bear a substituent selected from hydroxy, methoxy, t-butoxy, acetoxy, pivaloyloxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, 2-(dimethylamino)ethoxycarbonyl, cyano, methylsulfonyl, phenylsulfonyl, N-methylsulfonylcarbamoyl, N-phenylsulfonylcarbamoyl, N-(4-chlorophenylsulfonyl)carbamoyl, methylsulfonylamino, amino, dimethylamino, oxazolidin-2-on-3-yl, acetylamino, trifluoroacetylamino, ureido, methylsulfonyl, sulfamoyl, dimethylphosphoryl and diethylphosphoryl; and G is methyl, ethyl, benzyl, phenethyl, pyridyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl or 2-(pyridyl)ethyl, wherein an alkyl carbon may bear an oxo group and wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group G may bear a substituent selected from hydroxy, methoxy, acetoxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, phenylcarbamoyl, pyridylcarbamoyl, methylsulfonylamino, amino, dimethylamino, acetylamino, nicotinoylamino and trifluoroacetylamino.

4. A compound as claimed in Claim 1, 2 or 3 wherein R is sulfo, aminosulfonyl, dimethylaminosulfonyl, 2,2,2-trifluoroethylamino-sulfonyl, 2,2,2-trifluoroethylsulfonyl, trifluoromethylsulfonyl, methylsulfonyl (which may bear a methoxycarbonyl, carboxy or ethylsulfonyl substituent), methylaminosulfonyl, isopropylaminosulfonyl, butylsulfonyl, butylaminosulfonyl, tert-butylaminosulfonyl, cyclohexylaminosulfonyl, phenylsulfonyl

(in which the phenyl may bear a chloro, nitr , amino, acetylamino, trifluoroacetylamino, methoxy, carboxy, N-(4-chlorophenylsulfonyl)-carbamoyl or methylsulfonylamino substituent at the 3- or 4-position), anilino, pyridylsulfonyl, quinolinylsulfonyl, benzylsulfonyl (in which the phenyl ring may bear a nitro or amino substituent at the 3- or 4-position), pyridylmethyl-sulfonyl, 2-(pyridyl)ethylsulfonyl or benzylaminosulfonyl.

5. A compound as claimed in any one of Claims 1-4 in which R^5 is hydrogen and R^6 is hydrogen.

6. A compound as claimed in any one of Claims 1-4 in which R^5 is benzyl, the phenyl ring of which may bear a 3-fluoro, 4-fluoro, 4-trifluoromethyl, 4-methoxycarbonyl, 3-acetoxy, 3-hydroxy, 3-pivaloyloxy, 4-hydroxy, 4-pivaloyloxy, 3-trifluoroacetylamino or 3-amino substituent; and R^6 is hydrogen.

7. A compound as claimed in any one of Claims 1-4 in which R^5 is hydrogen; and R^6 is 2-furyl, 2-thienyl, 3-pyridyl or phenyl in which the phenyl may bear one or two halogeno, trifluoromethyl, methyl, hydroxy, methoxy, tert-butoxy, methoxycarbonyl or carboxy substituents.

8. A compound as claimed in Claim 7 wherein R^6 is phenyl, 4-fluorophenyl or 2-thienyl.

9. A compound as claimed in Claim 1 in which R^0 is isopropyl; R^5 is hydrogen; R^6 is phenyl; and R is 4-acetylaminophenylsulfonyl, 4-[N-(4-chlorophenylsulfonyl)carbamoyl]phenylsulfonyl, 4-[N-(2-methylphenylsulfonyl)carbamoyl]phenylsulfonyl or 2,2,2-trifluoroethoxycarbonyl.

10. A salt as claimed in Claim 1 selected from

(a) for an acidic compound of formula I, an alkalai metal salt, an alkaline earth metal salt, an aluminum salt, an ammonium salt, or a salt made from an organic base which affords a

pharmaceutically acceptable cation; and

(b) for a basic compound of formula I, an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion.

11. A method of making a compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1-10 which is characterized by:

(A) Oxidizing a corresponding alcohol of formula II;

(B) For a compound of formula I which bears a hydroxy substituent on an aryl or heteroaryl group, cleaving the alkyl ether or acyloxy ester of a corresponding compound of formula I which bears a lower alkoxy or lower acyloxy substituent on an aryl or heteroaryl group;

(C) For a compound of formula I wherein R is 2,2,2-trifluoroethoxycarbonyl or 2,2,2-trifluoroethylaminocarbonyl, acylation of a corresponding amine of formula V with 2,2,2-trifluoroethyl chloroformate or 2,2,2-trifluoroethyl isocyanate;

(D) For a compound of formula I wherein R is a sulfonyl group of formula D.W.SO^2-, sulfonylation of a corresponding amine of formula V with a corresponding sulfonic acid of formula D.W.SO_2.OH, or an activated derivative thereof;

(E) For a compound of formula I wherein R is a group G, substitution of the group X of a corresponding compound of formula G-X, wherein X is a conventional leaving group, such as for example halogeno, methylsulfonyloxy, trifluoromethylsulfonyloxy or diazonium, with a corresponding amine of formula V;

(F) For a compound of formula I which bears a group of formula COORa in which Ra is hydrogen (a carboxy group), decomposing the ester group of a corresponding ester made with a conveniently removed acid protecting group;

(G) For a compound of formula I which contains an amino N-H residue, removal by using a conventional method of the nitrogen pr tecting group of a corresponding compound bearing a conventional nitrogen pr tecting gr up, including for a compound f formula I

wherein R is G, the removal of an activating/protecting group Rx from a corresponding compound of formula Vb;

(H) For a compound of formula I bearing a moiety of formula COORa, CH_2COORa, CONRbRc, $CH_2CONRbRc$, $COO(CH_2)_2NReRf$ or $CONRdSO_2R^1$, acylation of a corresponding compound of formula HORa, HNRbRc, $HO(CH2)_2NReRf$ or $HNRdSO_2R^1$ with a corresponding acid of formula I bearing a moiety of formula COORa in which Ra is hydrogen, or an activated derivative thereof;

(I) For a compound of formula I bearing a lower acyloxy group or a group of formula NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCONRiRj or $NRkSO_2R^3$, acylation or sulfonylation of a corresponding compound of formula I bearing a hydroxy group or an amino group of formula NHRg, NHRh or NHRk (i.e. an amino group of formula NReRf is which Re is hydrogen and Rf is Rg, Rh or Rk) with an activated derivative of a corresponding acid of formula HOCHO, $HOCOR^2$, $HOCOOR^2$, HOCONRiRj (including an isocyanate or isothiocyanate) or $HOSO_2R^3$, respectively, using a conventional method;

(J) For a compound of formula I which bears a heteroaryl N-oxide group, oxidation of a corresponding compound of formula I which bears a heteroaryl group using a conventional oxidant; or

(K) For a compound of formula I which bears a primary amino group, reduction of a corresponding compound bearing a nitro group using a conventional reducing method; and

whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of an acidic or basic compound of formula I is required, by reacting the acidic or basic form of such a compound of formula I with a base or acid affording a physiologically acceptable counterion or by any other conventional procedure; and

wherein the chemical formulae I, II, V and Vb are set out hereinbelow; and

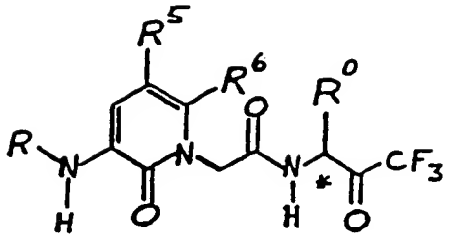
wherein each of R, R^0, R^5, R^6, D, V, G, Ra-Rn, R^1-R^3 and Q, except where more particularly described, has the meaning defined in any one of Claims 1-10.

12. A compound of formula II, set out hereinbelow, wherein R, R^0, R^5 and R^6 are defined as in Claim 1, or a salt thereof.

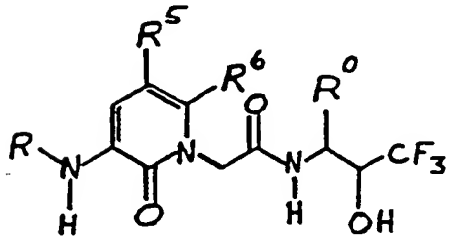
13. A compound of formula Vb, set out hereinbelow, wherein R has a value defined for G in Claim 1; R^0, R^5 and R^6 are defined as in Claim 1; and Rx is a group which protects and activates a primary amino group for substitution, or a salt thereof.

14. A pharmaceutical composition comprising a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

FORMULAE



I



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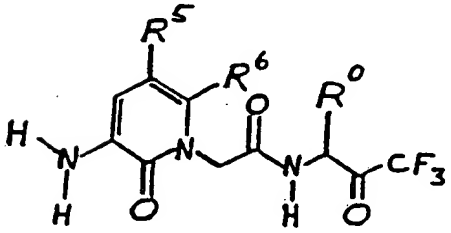

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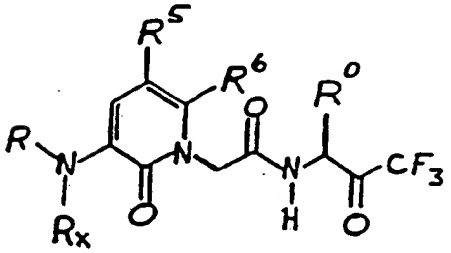

Vb

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00794

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K5/06; A61K37/64

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
P,X	EP,A,0 509 769 (IMPERIAL CHEMICAL INDUSTRIES PLC) 21 October 1992 see formulas I and II on page 85 see claims; examples	1-14
A	EP,A,0 369 391 (BOEHRINGER INGELHEIM PHARMACEUTICALS INC.) 23 May 1990 see page 2, line 15 - line 27; claims; examples	1,14
A	EUROPEAN JOURNAL OF PHARMACOLOGY vol. 193, no. 2, 7 February 1991, pages 153 - 158 C.P. SOMMERHOFF ET AL. 'Inhibition of human neutrophil elastase by ICI 200,355' see the whole document	1,14

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 JULY 1993	20 -08- 1993
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT OFFICE	FUHR C.K.B.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300794
SA 73122

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/07/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0509769	21-10-92	AU-A- 1482792	22-10-92
EP-A-0369391	23-05-90	CA-A- 2002819	15-05-90
		JP-A- 2256657	17-10-90